eman ta zabal zazu

Universidad del País Vasco

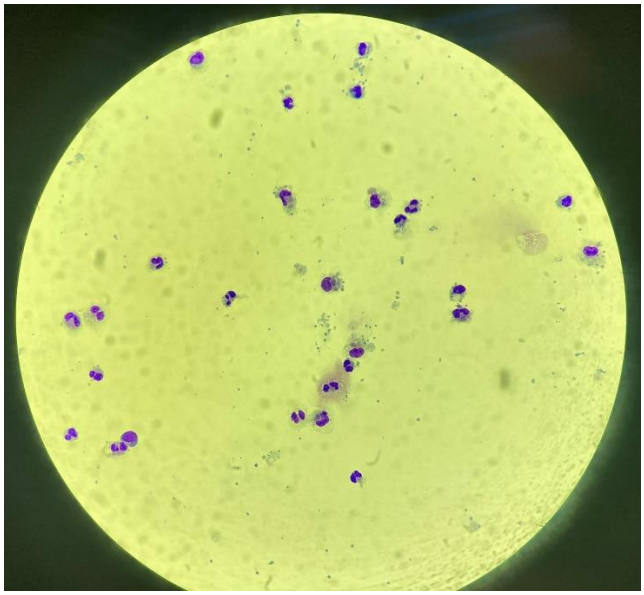
Euskal Herriko Unibertsitatea

NAZIOARTEKO BIKAINTASUN CAMPUSA

CAMPUS DE EXCELENCIA INTERNACIONAL

INFEKZIO BAKTERIANO INBADITZAILEEN IDENTIFIKAZIOA PEDIATRIAN, TXERTO KONBINATUEN GARAIAN

IDENTIFICACIÓN DE INFECCIONES BACTERIANAS INVASIVAS EN PEDIATRÍA EN LA ERA DE LAS VACUNAS CONJUGADAS



Egilea: Iker Gangoiti Goikoetxea

Zuzendariak: Santiago Mintegi eta Francisco Javier Benito

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ATXIKITAKO DERRIGORREZKO DOKUMENTUAK

HITZAURREA

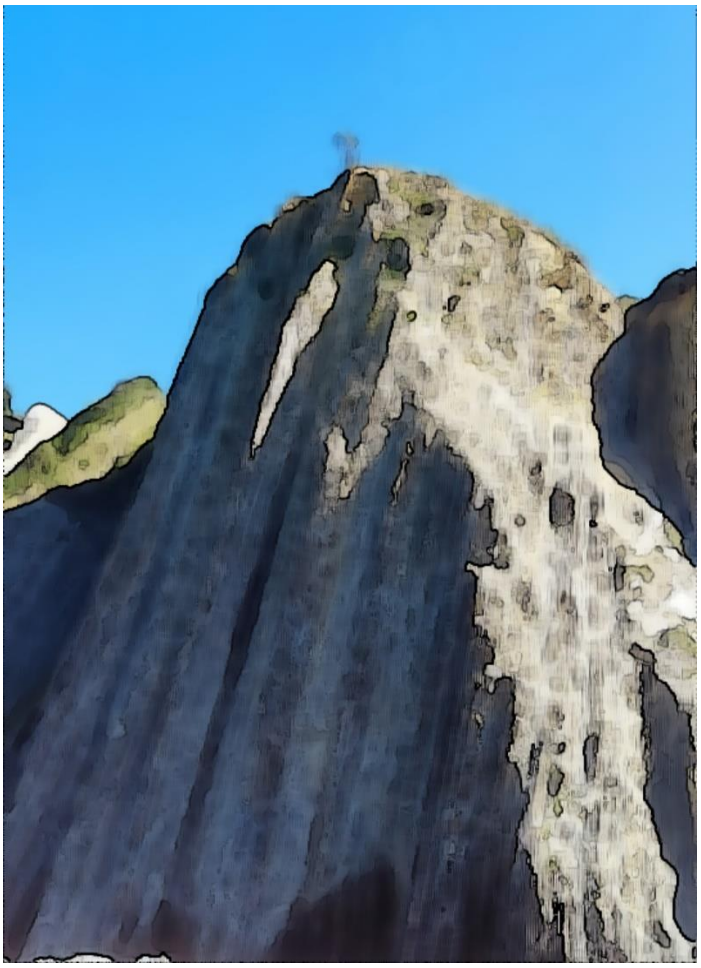
ATARIKOA

Tesi honen garapenean bizi momentu ugari igaro ditut, eta tesia berarekiko ere sentimendu kontrajarriak izan.

Azken urtean, nire tesiaren ibilbideak urratu asko utzi dizkidan lehengusinaren, AMAIAren bidearekin egin du aurrera. Irakaspenak alde askotatik etorri dira; baina etapa honetan aurrez gorespen handia nion artista baten presentzia jarraiak are bereziago egin du idatzi honen moldaketa.

Bertsolari, poeta, idazle, euskal abesti ugariren kantugile, itzultzaile, gidoilari, dokumentalgile, herrigile, historiadore eta istoriogile, eta bere gaixotasunarekin egin duen urte luzeko bidean, Amaiaren ondoan bidaiatu duen laguna; Jon Maiaz ari naiz. Azken proiektuen artean "Kantu bat gara"-k asko markatu ninduen ni eta zuen familia; nola lortu zuen kantuen letren bitartez norberaren eta herriaren bizitza kontatzea; nola eman ziezaiokeen bizia kantatzen jarri zuen herriari…aurretik ere arrailtzen ari zen zerbaitek krak egin zuen nire barruan.

Tesia euskeraz egiteko erabakia hartuta, Amaia eta Jon Maia berari zuzendutako keinu gisa eta nik neuk tesiarekin eta bizitako fase honekin adiskidetzeko behar dudan ariketa gisa, nire euskal talde kutunen (nire bizitzako soinu banda izan den Berri Txarrak, batik bat) kantuen zenbait letren hainbat esaldi esanguratsu kapituluz kapituluko sarreretan nahasiak izango dira.



Heldu herria sustraietatik,

tira eta gora jaso.

Jarri Kantauri aurrean eta

mantendu zutik hari so,

ispilu hortan ikus gaitezen

herriz-herri, auzoz-auzo.

Zauriak gatzez itxi ditzagun,

malkoak urez eraso,

sano ta libre irla ttiki bat

salbatuko gara akaso.

Jon Maia

HELDU DA GARAIA, ESKERTZEKO EMAN DIDAZUEN GUZTIA;
IRRIBARRE ONENAK ESNATZEN DITUGU GAUDENEAN.
ZUEKIN BATERA BERRIZ ASMATU NAHIKO NUKE BIZIA,
MAITE ZAITUZTEDALAKO NIRE ONDOAN (ETS).

Mila mila esker tesi hau aurrera eramaten lagundu didazuen bakoitzari. Idatzi hau aurrera atera bada, bi pertsonek dute batik bat "erru" nagusia: Santi nire zuzendariak eta nire amak, temati, oso temati, eta motibazioan egoskor, oso egoskor jardun dutelako. Eskerrik asko bihotzez.

Irakaspenak ere eman dizkit bide luze honek, medikuntzatik kanpo daudenak gehienbat gainera. Neurtu energía, hautazkoa den edozein erronkak gozatzea behar lukelako xede eta ez gainera etor dakioken elur jauziari beldur izatea.

Senaren bideak berpiztu eta hortik dela uste baduzu, ez pentsatu eta segi (ETS).

Baina, jakin, Orekak ez duela balio lurrean gaudenean (Btx).

Hala ere, zutik gaude, eta aurrez irudikatua nuen denbora tartea baino dexente gehiago igaro den arren, urteetako kantu edo tesi hau erditu dugu eta zuen ordua ere heldu dela (Eñaut Elorrieta eta Jon Maia) jakitun naiz: bidean ondoan izan zaituztedan guztiei aitortza egiteko ordua. Beste askoren artean…

Lorea eta Arette, izarrik argitsuenak; Aita eta Alatz, gehiagotan esan beharko nizueke maite zaiztuztedala; aitabitxi, lortzen dudan pausu bakoitzeko hor egon eta harrotu egiten zarelako; "pintxito" guztiak, Remen bereziki, garaiak, kaleak eta gu aldatu garen arren (Leihotikan) une gogorretan makulu izan zaretelako. Gurutzetako Larrialdi zerbitzuko familia, hor jarraitzen badugu hori sentitu dugulako izan delako, hor ere kaleak aldatu arren, "Bidailagunak infernuan, zeruan baino lehen" (Zetak); burua elkar torturatzea maite dogulako, Juanra (Te fuiste Allí, John O´Ray) eta nire bitamina, euste puntu eta babes izan zareten Itziar

eta Ainara, puskak biltzeko garaia delako, sentitzeko atertu duela (Mikel Urdangarin).

Javi tesiaren zuzendariari; eta tesi honek biltzen dituen artikuluetan autore eta kolaboratzaile izan zaretenoi nire esker ona, beste batzuen artean; Lorea, estatistikaren arduradun garrantzitsua eta nola ez, nirekin zuzenenan orpoz orpo aritutakooi: Borja (nire tutore), Maria, Patri, Juanra, Usune, Elva, Ane, Borja, Cata, Zaloa, Garazi, Libe eta orain, Ane.

AMA HIZKUNTZAN

AURKIBIDE OROKORRA

AURKIBIDE ZEHAZTUA

LABURDURAK

CDC: Gaixotasunen kontrol eta prebentziorako zentroa

DNA: azido desoxirribonukleikoa.

GIB: giza immunogutxiegitasunaren birusa.

IBI: infekzio bakteriano inbaditzailea.

KT: konfidantza tartea.

LZR: likido zefalorrakideoa.

PCR: polimerasan oinarritutako kate erreakzioa.

PCV7 eta PVC13: neumokokoaren aurkako txerto konjokatu zazpi eta hamahirubalentea.

RNA: azido erribonukleikoa.

SEUP: Pediatriako Larrialdietako Medikuntzako Espainiako Elkartea.

SIRS: Hantura Erantzun Sindrome Sistemikoa (Systemic Inflammatory Response Syndrome)

SAMR: metizilinari erresistentea den *S. aureusa.*

SOFA eskala: Sequential Organ Failure Assessment

LABURPENA

Zer esan, nola esan, aro eder honetaz? Sormenak, kemenak ezin esan dezakeenik (BTx)

LABURPENA

Sukarra ohiko kontsulta-arrazoia da larrialdi zerbitzu pediatriko batek artatzen dituen pazienteen artean. Kasurik ohikoenetan berez osatzen diren infekzio biralak daude jatorrian, baina batzuetan umeek infekzio bakteriano inbaditzaileak (IBI) pairatu ditzakete. IBIa diagnostikatzeko benetako bakterio patogeno batek izan behar du isolatua odolean edo likido zefalorrakideo, pleural edo artikularrean. Kezka gehien sortzen dituztenak odol eta likido zefalorrakideoan isolatutakoak izan ohi dira.

Tesi honen muina 2018 eta 2023 bitartean argitaratutako zortzi artikulu dira.

Sarreran, garai pediatrikoan IBIen gehiengoa sorrarazten duten bakterio ohikoenen zerrenda eta bakoitzaren ezaugarriak deskribatzen dira, IBI bakoitzak eragin ditzakeen kuadro kliniko ezberdinak banan-banan azalduz. Larrialdi zerbitzu pediatrikotik abiatu den tesi honetan, bertan lan egiten duen medikuak IBIa duen paziente bat identifikatzeko baliatu ditzakeen tresna multzoa ere deskribatzen da. Izan ere, tresna hauen erabilpenaren errentagarritasuna aldatzen joan da historian zehar, bai osasun munduan eta bai gizarte mailan eman diren aldaketen ondorioz; hauetako batzuen berri ere emango dugu sarreran.

Gure ustez, ezinbestekoa da aro pediatrikoan gertatzen diren IBIen egungo epidemiologia, aurkezpen modu eta hauen maneiuan zeresana duten baliabideen errendimendua ezagutzea, IBIen identifikazio eta tratamenduaren giltza izango diren diagnosi eta maneiu estrategia egokienak ezartzeko.

Lan hipotesi nagusia ondokoa da: IBIa pairatzen duen pazienteren karakterizazioak eta hauen identifikaziorako ditugun baliabideen errendimenduak aldaketak jasan izan dituela azken urteotan.

Helburu nagusiak hamalau urtetik beherako pazienteetan baieztatu diren IBIen aurkezpen klinikoaren karakterizazioa egin eta haien larritasuna deskribatzea izan ziren, tartean *E. coli*ak eta B taldeko estreptokokoak eragindakoena. IBIen identifikaziorako erabiltzen diren ohiko odol testen (leukozitoen zenbaketa, neutrofiloen zenbaki absolutua, proteina C erreaktiboa eta prokaltzitonina) balioa analizatzea eta fokurik gabeko sukarra duten eta larrialdi zerbitzura egonkor iristen diren 3-24 hilabete arteko haurrak ebaluatzerakoan odol testik ez erabiltzearen gomendioa analizatzea ere gure helburu nagusietako bat izan da. Tesi honen helburu zuzena ez zen arren, aurretik espero ez genuen pandemia batek larrialdi zerbitzu batean identifikatu diren IBIetan izan duen eragina ere deskribatu nahi izan dugu.

Horretarako, arestian esan bezala zortzi artikulu bildu ditugu lan honetan.

Lau argitalpen 2008an ireki zen prospektiboki erregistratutako data basean oinarritutako kohorte-ikerketa baten emaitza dira. Hirugarren mailako ospitale bateko larrialdi zerbitzu pediatriko batean, 14 urtetik beherako pazienteetan diagnostikatu diren infekzio bakteriano inbaditzaileak bildu ziren.

Gangoiti I, Valle JR, Sota M, Martinez-Indart L, Benito J, Mintegi S. Characteristics of children with microbiologically confirmed invasive bacterial infections in the emergency department. Eur J Emerg Med. 2018 Aug;25(4):274-280 artikuluan, zortzi urte bitarteko denboraldian 223 IBI identifikatu ziren, %83,9 kasutan aurrez osasuntsu ziren pazienteetan. Neumokoko eta meningokoko kasuak ia erdia izan ziren. Hala ere, pazienteen adina, karakterizazioa eta azken diagnosia, eragile izan zen mikroorganismoaren arabera aldatu ziren. Infekzio meningokozikoak izan ziren IBI larrienak. Gehienek ondo eboluzionatu arren, lau kasutan (%1,8) pazientea hil egin zen eta beste zortzik (%3,6) sekuela iraunkorrak pairatu zituen. IBIa larrialdietara egindako

bigarren bisita batean diagnostikatu zen 32 pazientetan (%14,3). Bigarren kontsultan IBIa diagnostikatu zitzaien 32 paziente horietatik lauk (%12,5) heriotza edo sekuela iraunkorrak pairatu zituzten. Gaixotasunaren lehenengo 24 orduetan larrialdi zerbitzuetan artatu izana, sukarraz gain beste sintomaren baten presentzia izatea eta larrialdi zerbitzura iristean ebaluazio pediatrikorako triangelu egonkorrik ez izatea larritasun handiagoa izateko arrisku-faktore independente definitu ziren.

Gangoiti I, Gorostizaga Z, Aranzamendi M, Gomez B, Benito J, Mintegi S. Repeated Emergency Department Visits Among Children with Invasive Bacterial Infections. Pediatr Infect Dis J. 2021 May 1;40(5) artikuluak, 14 urtetan zehar erregistratutako IBIak bildu zituen, 342. Horietatik aurrez osasuntsu ziren 271 pazientetan burutu genuen analisia. Ehun eta laurogeita hemeretzi pazientek (%73,4) antibiotiko parenterala jaso zuten lehen bisitan. Guztira, hamabost pazientetan larritasun irizpideak objektibatu ziren. Paziente hauetatik, zazpik ez zuten antibiotikorik jaso lehen bisitan.

Gangoiti I, Fernandez CL, Gallego M, Gomez B, Benito J, Mintegi S. Markers for invasive bacterial infections in previously healthy children. Am J Emerg Med. 2021 Oct;48:83-86 artikuluan, hamahiru urteko IBIak bildu ziren, 367ri orotara, baina analisia aurrez osasuntsu ziren 286 pazienteekin egin zen. Berrehun pazientek ebaluazio pediatrikorako triangelu egonkorra (%69,9) izan zuten larrialdi zerbitzura iritsitakoan. Azken diagnostikoak sepsia 64 (%22,4) kasutan, meningitisa 38tan (%13,3), bakteriemia ezkutua 63tan (%22,0) eta infekzio fokal inbaditzailea 121tan (%42,3) (arnas aparatuko infekzioa 46tan, gernu-aparatuko infekzioa 33tan, infekzio osteoartikular edo ehun bigunetako infekzioa 33tan eta beste batzuk 9tan) izan ziren. Isolatutako bakterio ohikoenak *Streptococcus pneumoniae* 89 (%31,1), *Neisseria meningitidis* 61 (%21,3),

Escherichia coli 40 (%14) eta *Staphylococcus aureus* 36 (%12,6) izan ziren (gainontzekoak 60, %21).

Oro har, 265ek (%92,7) odol balio anormal bat izan zuten gutxienez. Odol markatzaile bakoitzaren sentikortasuna azken diagnostiko eta bakterio eragilearen arabera aldatu zen. Sepsia eta meningitisaren kasuan prokaltzitonina eta C proteina erreaktiboaren sentikortasuna handiagoa izan zen; infekzio fokal inbaditzaileetan C proteina erreaktiboarena; meningokokoaren kasuan prokaltzitoninarena eta S. *aureus*aren kasuan C proteina erreaktiboaren sentikortasuna. Bakteriemia ezkutu neumokozikoa diagnostikotzat jaso zuten 3 eta 24 hilabete bitarteko adineko haurren odol-markatzaile bakoitzaren sentikortasuna ondokoa izan zen: prokaltzitonina %43,5 (%95 KT: 25,6-63,2); C proteina erreaktiboa %48,3 (%95 KT: 31,4-65,6); leukozitoen zenbaketa %75,9 (%95 KT: 57,8-87,8); neutrofiloen zenbaki absolutua %58,6 (%95 KT: 40,7-74,5).

Martin-Irazabal G, Gangoiti I, Gomez B, Lizarraga L, Mintegi S. Impact of the COVID-19 pandemic on pediatric invasive bacterial infections. An Pediatr (Engl Ed). 2023 Mar;98(3):228-229 artikuluan bi denbora tarte bereizi genituen pandemiaren deklarazioa ebaki-puntu hartuta. Pandemiaren aurreko aldian, 70 IBI diagnostikatu ziren eta 49 pandemian. Pandemia garaian, aurretiaz osasuntsu zen paziente baten IBI diagnostikatzeko probabilitatea nabarmen aldatu zen. Bestetik, pandemia garaiko IBIen erantzuleei dagokienez, aldaketak nabarmenak izan ziren; 2021ean *N. meningitidis* desagertu egin zen eta 2022an aldiz, *S. pneumoniae*ren hazkunde (9/22; diagnostikaturiko IBIen %40,9) handia eman zen. Hiru hilabetetik beherako haurrengan, B taldeko estreptokokoa izan zen IBIaren kausa nagusia pandemian ((%33,3) vs. *E. coli* (%50) pandemia aurreko garaian, $p<0,01$).

E. coli eta B taldeko estreptokokoaren karakterizazioa eta haien larritasunarekiko balizko harremana ikertzeko helburuz idatzitako artikuluak, aro pediatrikoan detektatzen diren bakteriemien karakterizazioa egitea helburu zuen erregistro prospektibo handi baten bigarren mailako analisien emaitza dira. 2010ean, Pediatriako Larrialdietako Medikuntzako Espainiako Elkarteak, gaixotasun infekziosoen lan taldea buru, Espainiako pediatriako larrialdi-zerbitzuetan isolatutako odol kultura positiboen erregistro multizentriko prospektibo bat ezartzea proposatu zuen. Haur jaio berri eta 20 urte bitarteko pazienteak prospektiboki erreklutatu ziren 2011 eta 2016 artean. Horietatik 1.696tan, benetako bakteria patogeno bat isolatu zen pazienteen odol laginean. Ikerketa hauen xederako, euren odol laginean *E. coli* eta B taldeko estreptokokoa isolatu ziren pazienteak aztertu ziren hurrenez hurren.

Elgoibar B, Gangoiti I, Garcia-Garcia JJ, Hernandez-Bou S, Gomez B, Martinez Indart L, Mintegi S; Bacteremia Study Working Group from the Infectious Diseases Working Group, Spanish Society of Pediatric Emergencies (SEUP). Paediatric KT: bacteraemia presentations and high-risk factors in the emergency department. Acta Paediatr. 2021 Mar;110(3):1032-1037 artikuluan *E. coli*ak eragindako 291 IBI identifikatu ziren. Jasotako diagnosi ohikoenak, gernu bideetako infekzio inbaditzailea 206 kasutan (%70,8), sepsia 32tan (%11) eta bakteriemia ezkutua 27tan (%9,3) izan ziren. Berrogeita hiru kasuk larritasun irizpideak bete zituzten (%14,8, % 95 KT: 11,2-19,3) eta horietatik bi hil egin ziren. Korrespondentzia anitzeko analisiek eta Cluster analisiek *E. coli* bakteriemia pediatriakoaren lau aurkezpen mota nagusi identifikatu zituzten. Lehen bi taldeak aurretik osasuntsu eta itxura ona zuten urtebetetik beherako haurrek osatu zuten, gernu bideetako infekzio inbaditzailearekin erlazionatuta eta bilakaera onarekin, oro har. Aurrez osasuntsu ez ziren 12 hilabetetik gorako pazienteek osatzen zuten hein handi batean hirugarren taldea; azken taldean adin ezberdinetako haurrak zeuden, herena ez zen

aurretik osasuntsu eta ebaluazio pediatrikorako triangeluaren arabera egonkor ez zeudenen proportzioa handiagoa zen gainontzeko taldeekin konparatuta. Bi talde horiek ez zeuden gernu bideetako infekzio inbaditzaileekin hainbeste erlazionatuta eta larritasun-tasak nabarmen handiagoak izan ziren, %15 eta %50,9 hurrenez hurren ($p<0,01$). Hildako bi pazienteak azken talde honen parte ziren.

Zortzi haurri meningitis bakterianoa diagnostikatu zitzaien, guztiak 5 hilabete baino gazteagoak. Hilabete batetik beherako *E. coli*-k eragindako bakteriemietan aurkitu zen meningitis tasa %9,4koa izan zen eta hilabete eta bi hilabeteko haurren artean %2,6koa. Bi hilabetetik gorako paziente bakarrean diagnostikatu zen meningitisa.

Ecclesia FG, Alonso Cadenas JA, Gómez B, Gangoiti I, Hernández-Bou S, de la Torre Espí M; Bacteremia Study Working Group from the Infectious Diseases Working Group, Spanish Society of PediatrICEmergencies. Late-onset Group B Streptococcus Bacteremia Evaluated in the Pediatric Emergency Department and Risk Factors for Severe Infection. Pediatr Infect Dis J. 2022 Jun 1;41(6):455-459 artikuluan B taldeko estreptokokoak eragindako 134 IBI bildu ziren. Pazienteen %14,4ean baino ez zen aurkitu arrisku faktoreren bat. Infekzio larria diagnostikatzeko odol markatzaile ezberdinen analisien sentikortasunari dagokionez, ez da esanahi estatistikorik aurkitu nahiz eta prokaltzinoninaren 0,5ng/ml baino handiagoak diren balioak infekzio larrietan maizago aurkitu. Infekzio larritzat hartu zirenetatik (sepsia edo meningitisarekin diagnostikatu zirenak, 74 guztira), 15ek baino ez zuten ebaluazio pediatrikorako triangelu egonkorra izan larrialdi zerbitzuan artatuak izan zirenean. Aldagai anitzeko ereduan oinarrituta, esanahi estatistikoa lortu zuen infekzio larriarekin lotutako oinarrizko arrisku-faktore bakarra ebaluazio pediatrikorako triangeluan oinarritutako egoera ez egonkorra izan zen. Sei pazientetan bilakaera ez zen ona izan (%5,1), denek izan zituzten konplikazio akutu

larriak (%5,1), bik sekuela iraunkorrak izan zituzten eta beste bi hil egin ziren. Sei pazienteak 26 egun baino gazteagoak ziren, triangeluaren arabera ez zeuden egonkor, prokaltzitoninaren balio altuak zituzten; horietatik leukopenia lau pazientetan identifikatu zen.

Fokurik gabeko sukarra duten eta larrialdi zerbitzura egonkor iristen diren 3-24 hilabete arteko haurrak artatzerakoan odol testik ez erabiltzearen gomendioa ebaluatu duten artikuluak metodologia ezberdina garatu zuten bi lanen emaitzen ondorio dira.

Gangoiti I, Rodriguez E, Zubizarreta A, Benito J, Mintegi S. Prevalence of Occult Bacteremia in Infants With Very High Fever Without a Source. Pediatr Infect Dis J. 2018 Nov;37(11):e271-e273 artikulua, atzera begirako ikerketa deskribatzaile eta analitikoaren emaitza da, Osasun Publikoko Sistemaren parte den hirugarren mailako irakaskuntza ospitale baten larrialdi zerbitzu pediatrikoetan burututakoa. Ikertutako populazioa, 2013ko urtarriletik 2016ko abendura arteko larrialdi zerbitzu pediatrikoan artatutako 3-24 hilabete bitarteko eta egonkor zeuden haur osasuntsuak izan ziren, etxean edo ospitalean 40,5ºCko tenperatura edo altuagoa objektibatu zitzaien paziente taldea. Emaitza aldagaia odol laginean egin zen benetako bakterio patogeno baten identifikazioa izan zen. Guztira 543 odol kultura eskuratu ziren; ondoren, sukarraren jatorria ezaguna edo ezezaguna izatearen araberako analisia egin zen. Fokurik gabeko sukarra zuten 363 haurren arteko bakteriemia ezkutuaren prebalentzia %1,1ekoa (%95 KT: 0-2,2) zela kalkulatu zen. Guztien bilakaera ona izan zen.

Gangoiti I, Zubizarreta A, Elgoibar B, Mintegi S; Infectious Diseases Working Group, Spanish Society of Pediatric Emergencies (SEUP). Occult bacteremia in young children with very high fever without a source: a multicenter study. Pediatr Infect Dis J. 2020 Dec;39(12):e462-e464 artikulua zentro anitza den ikerketa prospektiboa da. Espainiako

pediatriako larrialdietako sei zerbitzutan artatu ziren, aurretiaz osasuntsu ziren eta 40,5ºC edo tenperatura altuagoa zuten fokurik gabeko sukardun pazienteen kohorte baten oinarritua. Pazienteak prospektiboki bildu ziren 2018ko urtarrilaren 1etik 2019ko abenduaren 31ra arte. Ikerketa unizentrikoan planteatu ziren inklusio kriterioak, maneiu terapeutikoak, definizioak eta emaitza aldagaia berberak dira.

Guztira 203 paziente bildu ziren eta 31 pazientetan larria izan zitekeen infekzio bakterianoa diagnostikatu zen: gernu-infekzioa 14tan (%6,9), neumonia 11tan (%5,4) eta bakteriemia 6tan (%3). Bakteriemia ezkutua diagnostikatu zitzaien 6 haurretatik 3tan neumokokoa isolatu zen; bakteriemia ezkutu neumokozikoaren prebalentzia %1,48koa (%95 KT: 0,5-4,3) zela kalkulatu zen. Paziente guztien eboluzioa ona izan zen.

Tesi honetan bildutako artikulu guztiek hipotesian azaldu diren ideien garrantzia azpimarratzen dute eta IBIen inguruan egin beharreko ikerkuntza eta zaintza jarraiak ezinbesteko jarduera behar luke halako gaixotasun bat paira dezakeen ume eta nerabeari eskain dakiokeen kalitaterik handieneko arreta eskaintzeko. Nahiz eta tesiaren muinean ez egon, COVIDak gure inguruan diagnostikatu diren IBIetan izan duen eraginak aurreko guztia baino ez du berresten.

SARRERA

Ongi etorria naufragoei, asteroideen antzokira (Kerobia)

Ez dakit zenbat denbora daramadan hemen! (Izaro)

Zuen arnasa lepoan, bidea hasi dadila (ETS)

SARRERA

Sukarra ohiko kontsulta-arrazoia da larrialdi zerbitzu pediatriko batek artatzen dituen pazienteen artean[1].

Egia da kasurik ohikoenetan berez osatzen diren infekzio biralak daudela jatorrian. Dena den, batzuetan umeek infekzio bakteriano inbaditzaileak (IBI) paira ditzakete. IBIa diagnostikatzeko benetako bakterio patogeno batek izan behar du isolatua odol, likido zefalorrakideo, pleural edo artikularrean. Kezka gehien sortzen dituen IBIa odol eta likido zefalorrakideoan isolatutakoa izan ohi da. Horregatik, sepsia eta meningitisa alde batera utzi ezin daitezkeen heriotza arrazoiak dira oraindik ere herrialde garatuetan[2], nahiz eta azken hamarkadetako baldintza eta txerto eta antibiotikoen arloan egindako ikerketek aurrerapauso garrantzitsuak ekarri. Honek guztiak, orain ez urte asko infekzio larrien erantzule ziren bakterio ohikoenen isolamenduaren jaitsiera nabarmena eragin du. Bestalde, herrialde garatuetan, agerikoa da pazienteak artatzeko osasun zerbitzuen irisgarritasunak gora egin duela eta haurrak prozesu infekzioso oso goiztiarrekin egiten dutela kontsulta, bai larrialdi zein lehen mailako arreta zerbitzuetan[3]. Oso ohikoa da, baita ere, paziente hauen adina 2-3 urtetik beherakoa izatea; kuadro klinikoaren adierazkortasunean aldaketak eragin ditzake eta bistara egon ohi ziren ezaugarri, zeinu eta sintomak hain agerikoak ez izatea bultzatu[4]. Gainera, paziente pediatrikoa artatzen duen profesional medikuaren profilak aldakortasun oso handia du; lehen urteko mediku egoiliar batetik paziente helduak artatu ohi dituen lehen arretako familia mediku batera. Ekuazio honen aldagai guztiek infekzio bakteriano inbaditzailearen identifikazioan eragina dute.

Txertaketa kanpainen eragina ez du inork jada zalantzan jartzen. Honela, argi ikusi da mende aldaketarekin etorri zen *Haemophilus influenzae b*ren aurkako txertaketa

unibertsalak ondorio zuzena izan zuela lehen munduko haurrengan identifikatzen ziren infekzio inbaditzaile larrienetan[5]; hauen desagertze ia erabatekoa ekarri zuen txertatutako populazioan. Honekin batera *Streptococcus pneumoniae*ren aurkako txerto konjokatuen merkaturatzeak infekzio inbaditzaile neumokozikoen jaitsiera nabarmena ekarri du[3,6,7,8,9].

Ohikoa zen txerto hauen komertzializazioa baino lehen, aurrez osasuntsu ziren eta ebaluatzerako orduan itxura ona zeukaten bularreko haurren proportzio txiki batean, sukarra zela eta kontsultatzen zutenen artean, odolean bakterio bat isolatzea (ezkutuko bakteriemia), *H. influenzae* lehenago eta *S. pneumoniae* gerora batik bat[10]. Artikulu klasikoen arabera, populazio baten bakteriemia ezkutuaren prebalentzia esanguratsua zenean, egun baino handiagoa, 39ºCtik gorako fokurik gabeko sukarra duten 3-24 hilabete bitarteko haurretan[11] odol kultura bat egitea gomendatzen zen. *H. influenzae B* eta *S. pneumoniae*ren kontrako txertoen ezarpena eta gero, prebalentzia honek behera egin du nabarmen[12], eta errutinazko bilaketa bat egitea ez legoke guztiz gomendatua, gutxienez neumokokoaren aurkako txertoaren dosi bi jaso dituzten paziente hauetan[4,13,14,15,16,17,18]. Aitzitik, gaixotasun honen prebalentziak %0,5etik behera egiten duenean, testatzen diren odol frogen errendimenduak, leukozitoen zenbaketak eta neutrofiloen zenbaki absolutuak kasu, behera egiten du nabarmen[11,19]. Izan ere, Lee-k argitaratu zituen datuen arabera, odol proben errendimendu handiena ezkutuko bakteriemiaren prebalentzia %1,5etik gorakoa denean ematen da.

Bakteriemia ezkutuaren prebalentziak gora egiten duela ere deskribatu izan da hauteman den tenperaturaren balioak gora egiten duenean[5]; sarri erlazionatu dira tenperaturaren gradazioa eta paziente talde honetan identifikatzen zen ezkutuko bakteriemiaren prebalentzia. Talde honek, oso tenperatura altua duten umeen taldeak alegia, berarekin

dakartzan berezitasunek zalantzak sorrarazten dituzte pazientearen ohe buruan dagoen edozein profesionalengan.

Bestetik, azken hamarkada bietan *N. meningitidis*ak sorrarazitako infekzio inbaditzaileen kopuruak nabarmen egin du behera[20,21], hein handi batean C serotaldedun *N. meningitidis*aren aurkako txertoaren unibertsalizazioak ere antzeko eragina izan baitu. *N. meningitidis*ak eragindako infekzio inbaditzaileen kasuan B serotaldea izan da azken urteetan herrialde garatuetan aldaera nagusia. Hala ere azken urteotan beste aldaera batzuek gora egin dute, W eta Y aldaerek batik bat, B serotaldearen joera oro har nahiko egonkor mantendu delarik. Azken urte hauetan, gainera, *N. meningitidis*aren aldaera ezberdinen aurkako txertoak agertu dira merkatuan. Espainiar Pediatria Elkartearen baitan dagoen Txertoen Aholkularitza Batzordeak jadanik gomendatu ditu[22] eta zenbait Autonomia Erkidegok sartu dituzte jada jaio osteko estrategia finantziatuaren barruan (Euskal Autonomia Erkidegoan, 2023 urtean jaiotako haurrak baliatu dira neurri honetaz); honek izango duen eragina, momentuz, ikusteko dago.

Aldaketa epidemiologiko guzti hauek infekzio bakteriano inbaditzaileen murrizte garrantzitsua ekartzeaz gain, eragile nagusi diren mikroorganismoen sakabanaketa zabalagoa eragin dute. Egun, garrantzitsuenetakoa *E. coli*a da. Bera da urtebetetik beherako haurrengan bakteriemia gehienen erantzulea, batik bat hiru hilabetetik beherako pazienteetan jakinarazia eta oro har, gernu bideetako infekzioekin erlazionatuta dagoena[23]. Hala ere, gure inguruan ez zen bakteriemia honen ezaugarri kliniko nahiz ondoriorik aztertzen zuen lagin handidun ikerketarik egin. Pentsatzekoa zen gainera bakteriemia hau pairatzen duten pazienteen profil ezberdinak existituko zirela eta profil bakoitza arrisku maila ezberdin batekin erlazionatuta egotea.

Horregatik, ez da harritzekoa IBI bat izan dezakeen haurraren identifikazio goiztiarra beti ez lortzea. IBIen azken urteotako gainbeherari, artatzen diren pazienteen ezaugarrien aldaketei (pazientea, kuadro klinikoen zeinu eta sintoma klasikoak agertu aurretik artatu ohi da larrialdi zerbitzu baten) larrialdi zerbitzu batean haurra artatzen duten profesionalen aldakortasun handia gehituz gero, arazo honen azaleratzea baino ez du erakutsi. Ikerketa batek baieztatu zuen meningitis bakteriano edo sepsia pairatu duten paziente pediatrikoen %22a behin baino gehiagotan izan zirela artatuak larrialdi zerbitzu batean[24], azken emaitza eta ondorioak lehen kontsultan identifikatutako haurren antzekoak izan zirela nabarmendu zuten arren[25].

Hala ere, sepsi pediatrikoaren maneiurako gidek zain barneko tratamendu antibiotiko azkarra giltzarria dela azpimarratu izan dute; are gehiago, lehen ordua funtsezkoa da shock egoera bistaratu denean[26]. Horregatik, paziente talde jakin baten aurrean, odol analisi eta biomarkatzaileek eragiten duen erantzuna IBIa identifikatzeko erabakitze prozesuaren parte den tresna garrantzitsu bihurtzen da. Baina IBIen erantzule izan ohi ziren mikroorganismo sortaren aldaketa eta pazientearen artatze prozesua gero eta goiztiarragoa dela kontutan hartuz gero, test hauen errendimendu eta erantzuna aurretiaz publikatutakotik ezberdina izan daitekeela ondoriozta daiteke. Eskuarki, leukozitosia eta neutrofilia izan dira larrialdi zerbitzu pediatriko baten erabakiak hartzeko parametro analitiko erabilienak, eta berrikiago, C proteina erreaktiboa. Azken urteotan, gainera, prokalzitoninak balio biokimiko erabilgarri gisa jardun du, markatzaile klasikoen aldean abantailak eskaintzen baititu[16,17,27,28]. Hala ere, biomarkatzaile berriak agertze eta gehitzeak batzuetan zaildu egin dezake IBIa izateko arrisku handiena duten pazienteak identifikatzea[19], IBI guztiek ez baitute erantzun bera odol biomarkatzaileetan.

IBIEN SAILKAPENA

Sarreran aipatu bezala, IBIaren diagnostikoa odol, likido zefalorrakideo, likido pleural edo likido artikularrean egindako benetako bakterio patogeno baten isolamenduan oinarritzen da. Dena den, isolamendua garatzen den likidoaren, ostalariarengan duen eraginaren eta ostalariak berak duen erantzunaren arabera, oso egoera kliniko ezberdinak sor daitezke.

Bakteriemiaren definizioa odol lagin batean egiten den benetako bakterio patogeno baten isolamenduan datza. Benetako bakterio patogenoak, klasikoki kontaminante gisa definitzen diren mikroorganismoak alde batera uzten ditu, hala nola *Staphylococcus epidermidis, Propionibacterium acnes, Streptococcus viridans, Corynebacterium spp.*, eta bestelako difteroideak. Klasikoki kontaminante deritzen mikroorganismoek ere eragin ditzakete bakteriemiak aurretiaz osasuntsu ez diren pazienteetan: gaixotasun onkologiko bat edo bestelako inmunogutxiegitasuna jasaten duten haurrak, kateter zentral edo deribazio balbula baten garraiatzaile diren pazienteak, teknika diagnostiko edo terapeutiko inbaditzaileak burutu diren pazientea teknika egin eta ondorengo egunetan…

Bakteriemien barruan talde handi bi bereiz ditzakegu: infekzio fokal batek sorturikoak (infekzio fokal inbaditzaileak) eta infekzio fokalik gabekoak (bakteriemia ezkutua).

Haien garrantzi eta larritasuna, eta ezinbestean atxikitutako hilkortasun eta morbilitate tasak direla eta, meningitisa (infekzio fokal inbaditzailea) eta sepsia (infekzio barreiatua, jatorri infekzio fokal ezagun edo ezezagun bat izan dezakeena) beren-beregi aparteko era baten azalduko ditugu.

Meningitis bakterianoa

Meningitisa meningeen hanturari deritzo, piamadre, araknoide eta gune azpiaraknoideari erasaten diena. Etiologiari dagokionez, aro pediatrikoan jatorri birala izatea da ohikoena; enterobirusa, batik bat, pronostiko oso ona duena. Bakterianoa izatea, likido zefalorrakideoan hazten den bakterio baten isolamenduak mugatuko du. Egoera hau, oro har, mukosen geruzak kolonizatu dituzten organismoek odol-zirkulazioa inbaditu ostean gertatzen da.

Azken urteotako txertaketa kanpainek eta B taldeko estreptokokoaren inguruan egiten den profilaxi antibiotikoak meningitis bakterianoaren epidemiolologia erabat aldatu dute. B taldeko estreptokokoa eta bazilo Gram negatiboak izango dira meningitis bakterianoaren eragile hiru hilabetetatik beherako haurretan eta *Streptococcus pneumoniae* eta *Neisseria meningitidis* adin honetatik gorako haur osasuntsuetan[29,30,31,32,33].

Kasu gehienetan, odol hodietan zehar barreiatu eta hesi hematoentzefalikoa zeharkatu ostean araknoide azpiko gunera igaro ohi dira bakterioak. Behin nerbio sisteman ezarria, erreplikazio esponentzial baten eta hantura sortzen duten bitartekari ugari sortu ostean, ehunaren behin betiko lesioa sorraraziko duen prozesua hasiko da. Nahiz eta meningitisaren patogenian mekanismo honek izan indarrik handiena, sudur sinu batetik edo erdiko belarri bidetik hasitako, eta mastoide hezurra eroale delarik gertatzen den hormaz hormako zuzeneko hedapenak ere eragin dezake kuadro kliniko hau. Bestelako zenbait egoerek, likuorrea agertzen den kraneo-haustura batek edo zauri sarkari nahiz neurokirurgiako prozedurek ere erraz dezakete meningitis bat garatzea.

Klinika, meningitisa pairatzen duen haurraren adinak, mikroorganismo eragileak, eboluzio denborak eta pazientearen erantzun immunologikoak definituko ditu. Jaioberri

eta bularreko haur gazteetan, klinika ezohikoa eta espezifikotasun gutxikoa izaten da: suminkortasuna, jan nahi ez izatea, motelago egotea, sukarra ala hipotermia, zianosia, baita apnea bera ere. Bularreko haur nagusiagoen sintomak ere oso inespezifikoak dira, sukarra izan ohi da ia kasu gehienetan, suminkortasuna, letargia, gorakoak, jateari errefusa bestelako zeinu eta sintomez gain. Ume nagusi eta nerabeetan ikusiko lirateke sintoma klasikoenak: sukarra, gorakoak, fotofobia, buruko mina…

Meningitisa pairatzen duen pazientearen azterketa fisikoan nabarmendu daitezkeen zeinu klinikoak ere askoz inespezifikoagoak izango dira jaioberri eta bularreko haur txikiengan. Fontanela neurriz handituta edo puztuta egotea garezur barneko hipertentsioaren adierazle da; zeinu berantiarra da eta klasikoki nabarmendu den arren, gaur egunean ez da sarriegi ikusten. Honela, Martinez et alen[32] ikerketa baten arabera, hiru hilabete baino gazteago ziren eta meningitisa zuten 11 haurren artean fontanela normala zen hamarretan (bestearen azterketan ez zen adierazi fontanelaren egoera). Ume nagusiagoetan hauteman daitezke meningitisaren zeinu klasikoenak: Kernigena (aldakaren flexioak eragiten duen garondoaren erantzun zurruna) eta Brudzinskirena (garondoak berak, bere flexioaren saiakera egitean eskaintzen duen erantzun zurruna). Garondoaren zurruntasuna bera ere ez da meningitisaren zeinu patognomonikoa, beste prozesu batzuetan ere deskribatu izan direlako, hala nola neumonia, faringoamigdalitisa edo gastroenteritisa bezalako gaixotasunen bilakaeran[34,35]. Hala ere, zeinu hauen agertze hutsak meningitisaren presentziaren aukera handitu egiten du berau baztertzeko probak burutzea ia ezinbesteko izango delarik[30,34,36].

Meningitisaren zeinu-sintomek osatzen dituzten ereduen deskripzio klasikoek ere lagun dezakete bere jatorriaren identifikazioan. Meningitis bakterianoek sorturikoen baitan bi eredu nabarmendu izan dira. Bat, hasiera bortitz eta bilakaera jarrai eta azkarra duena eta

shock, purpura, odol hodietako koagulazio barreiatua, konorte gutxitzea,… eragin dezakeena eta 24 orduren bueltan heriotza; bigarrena, zerbait nahasiagoa, egun batzuetako sukarraren ondotik datorrena, arnas sistema edo liseri aparatuko sintomez lagundua eta progresiboki nerbio sistema zentraleko zeinuak agerian utziko dituena, hala nola suminkortasuna edo letargia.

Sepsia

Egun pediatrian ez da komunitate zientifiko osoak onartuko duen definizio jakin bat zehaztu; oro har, infekzio baten aurka organismoak ematen duen erantzun immune desegokiak disfuntzio organikoa eragiten duenean sepsiaz arituko gara[37].

Izan ere, pediatrian onartu zen azken definizio arautua, 2005 urtean egin zen Sepsi Pediatrikoaren Adostasunerako Nazioarteko konferentzian erabakitakoa da[38]. Honen arabera, organismoak, balizko infekzio edo/eta baieztatutako infekzio baten aurrean ematen duen hantura-erantzun sindrome sistemikoa da sepsia. Hau neurtzeko SIRS (Systemic Inflammatory Response Syndrome/Hantura Erantzun Sindrome Sistemikoa) puntuazio eskala erabiltzen da, infekzioa egon ala ez ager daitekeena eta ondorengo kriterioak dituena: bestela ondorioztatu ezin daitekeen eta adinari atxikitako takikardia (bradikardia urte betetik beherako haurrengan), takipnea adinari atxikia, edo bentilazio mekanikoaren beharra duen arnas prozesu akutua; 38,5ºCtik gorako edo 36ºCtik beherako tenperatura eta leukozitoen zenbaketa anormala (leukozitosia edo leukopenia) edo neutrofilo heldugabeen %10etik gorako zenbaketa; gainera, nahitaezkoak izango dira tenperatura edo odol analisitik eratorritako kriterioak[26,38].

Egia da SIRS kriterioak oso kritikatuak izan direla sortu zirenetik. Ez dauka sepsia bezalako larritasuna duen kuadroaren diagnostikoa egiteko behar besteko

baliagarritasunik eta ondorioz, hilkortasun tasa aurreikusteko sentikortasun eta espezifikotasun maila apala da. Horregatik sarri erabilia izan da adostasun dokumentu honetan onartu zen "sepsi larri" kontzeptua[38]. Honetan, sepsiaren definizioari kriterio hauek gehitu zitzaizkion: disfuntzio kardiobaskularra, arnas zailtasun sindrome akutua edo/eta bestelako bi sistemen disfuntzioa. Shock septikoa, 40ml/kg-rainoko likido isotonikoen administrazioak egonkortzen ez duen sepsi eta disfuntzio organikoa bezala definitu zuten.

Guzti honek bultzatuta, 2016an Surviving Sepsis Campaign-ek *"Sepsis-3, Nazioarteko hirugarren adostasun dokumentua"*[39] publikatu zuen, paziente helduari zuzendua. SIRS kriterioak alboratu eta sepsis eta shock septikora sinplifikatu zituzten definizioak, sepsi larria desagerraraziz. Sepsia, hitzarte honen hasieran erakutsi den erara definitzen dute: infekzio baten aurka organismoak ematen duen erantzun immune desegokiak sorrarazi eta bizia arriskuan jartzen duen disfuntzio organikoa. Disfuntzio organiko honen balorazioan SOFA eskala (Sequential Organ Failure Assessment) erabiltzen da, eta 2 edo 2tik gorako puntuazioa izatekotan definituko da sepsia.

SOFA eskala (Sequential related Organ Failure Assessment)

	0	1	2	3	4
Arnas parametroak PaO_2/FiO_2 (mmhg) o SaO_2/FiO_2	>400	<400 221-301	<300 142-220	<200 67-141	<100 <67
Koagulazioa Plaketak ($10^3/mm^3$)	>150	<150	<100	<50	<20
Gibel parametroak Bilirrubina (mg/dl)	<1,2	1,2-1,9	2,0-5,9	6,0-11,9	>12,0
Kardiobaskularra[b] Tentsio arteriala	Bataz besteko TA≥70mmHg	Bataz besteko TA<70mmHg	Dopamina <5 edo dobutamina edozein dositara	Dopamina 5-15; adrenalina <0,1 edo noradrenalina ≤0,1	Dopamina>15; adrenalina >0,1 edo noradrenalina >0,1
Nerbio sistema zentrala Glasgow eskala	15	13-14	10-12	6-9	<6
Iraitz sistema Kreatinina mg/dl Gernu fluxua (ml/egun)	<1,2	1,2-1,9	2,0-3,4	3,5-4,9 <500	>5 <200

***PaO_2**, oxigenoaren presio partzial arteriala; **FiO_2**, arnastutako oxigenoaren frakzioa; **SaO_2**, oxigeno periferikoaren saturazio arteriala. **b**, Bataz besteko tentsio arteriala >65mmhgtik gora mantentzeko sendagai basoaktiboen beharra gutxienez ordu betean (unitateak mikrogramo/kg/min*)

Shock septikoa aldiz, laktatoa > 2mmol/l-tik gora eta droga basoaktiboen beharra duen hipotentsio iraunkorra sortzen duen disfuntzio kardiobaskularra elkartzen direnean definituko da.

Azken urteotan saiakera asko egin dira definizio hauek arlo pediatrikora moldatzeko eta p-SOFA deritzon eskala ere planteatu da[40].

P-SOFA Taula

	0	1	2	3	4
Arnas parametroak PaO_2/FiO_2 edo $SatO_2/FiO_2$	≥400 ≥292	300-399 264-291	200-299 221-264	Arnas euskarriarekin 100-199 148-220	Arnas euskarriarekin <100 <148
Koagulazioa Plaketak (zelula/mm^3)	≥150.000	10.000-149.000	50.000-99.000	20.000-49.000	<20.000
Gibel parametroak Bilirrubina (mg/dl)	<1,2	1,2-1,9	2,0-5,9	6,0-11,9	>12,0
Kardiobaskularra PAM (mmHg) edo droga basoaktiboen beharra (mkg/Kg/min)	PAM <1 hile(h): ≥46 1-11h: ≥55 12-23h: ≥60 24-59h: ≥62 60-143h: ≥65 144-216h: ≥67 >216h: ≥70	PAM <1h: 46 1-11h: <55 12-23h: <60 24-59h: <62 60-143h: <65 144-216h: <67 >216h: <70	Droga basoaktiboen beharra: Dopamina ≤5 edo dobutamina (edozein dosi)	Droga basoaktiboen beharra: Dopamina 5-15 edo adrenalina ≤0,1 edo noradrenalina ≤0,1	Droga basoaktiboen beharra: Dopamina >15 edo adrenalina >0,1 edo noradrenalina >0,1
Neurologikoa Glasgow eskala	15	13-14	10-12	6-9	<6
Iraitz sistema Kreatinina (mg/dl) <1 hile 1-11 hile 12-23 hile 24-59 hile 60-143 hile 144-216 hile >216 hile	<0.8 <0.3 <0.4 <0.6 <0.7 <1.0 <1.2	0.8-0.9 0.3-0.4 0.4-0.5 0.6-0.8 0.7-1.0 1.0-1.6 1.2-1.9	1.0-1.1 0.5-0.7 1.6-1.0 0.9-1.5 1.1-1.7 1.7-2.8 2.0-3.4	1.2-1.5 0.8-1.1 1.1-1.4 1.6-2.2 1.8-2.5 2.9-4.1 3.5-4.9	≥1.6 ≥1.2 ≥1.5 ≥2.3 ≥2.6 ≥4.2 ≥5

Hala ere, sepsi pediatrikoaren azken eguneratze dokumentua 2020an publikatu da eta ez du 2005eko definiziotik eraldaketa adierazgarririk izan[41]. Zainketa berezien unitateetan burututako ikerketen arabera, pSOFA eskalak SIRS kriterioak baino baliagarriago dela ematen du, bai disfuntzio organikoa definitzerakoan eta bai heriotza tasen aurreikuspena egiterako orduan[42].

Halaber, laborategi kriterioek batik bat, asko baldintzatzen dute eskala honen erabilpena larrialdi zerbitzu pediatriko baten eta horregatik bere erabilpena ez dago hedatuta

ingurune honetan. Oraindik ere, inguruko elkarte zientifiko pediatrikoak erabilgarri izango den definizio bat adostu nahian lanean ari dira.

Epidemiologiari dagokionez, aurretiaz aipatutako bakteriak izango dira erantzule nagusi osasuntsu diren pazienteetan. B taldeko estreptokokoa izango da shock septikoen erantzule nabarmenena haur gazteenetan eta *N. meningitidis* 3 hilabetetik gorako pazienteetan [43,44,45,46].

Infekzio fokal inbaditzaileak

Gernu-bideetako infekzioa

Zeinu eta sintoma jakin batzuei gernu bideetan isolatutako bakterio kopuru esanguratsu bat gehitzen zaizkionean gernu infekzio baten aurrean gaudela esango dugu. Behin betiko diagnostikoa leukozituria agertzeak eta gernu analisian egindako kulturaren positibatzeak zehaztuko dute.

Gernu infekzioei buruz hitz egiten dugunean bi kuadro kliniko bereiziko ditugu. Pielonefritis akutua deritzo goiko gernu bideei eragiten dien infekzioari; sukarra izan ohi du, 38,5ºCtik gorakoa, odol markatzaile biologikoen areagotzea (hala nola, leukozitosia, neutrofilia edo sedimentazio globularraren abiadura, C proteina erreaktiboa eta prokaltzitoninarena) eta giltzurruneko balizko lesio atzeraezina ekar dezake, kortexeko orban modura. Zistitisa, beheko gernu-bideei eragiten dien infekzioa da, sukarrik gabekoa oro har, eta txiza egitean ezinbestean atxikitzen zaizkion sintomei lotua (mina, polakiuria, hematuria…). Ez du giltzurrunean orbanik eragingo.

Gernu-bideetako infekzioa pairatzen duten bularreko haurren zeinu nagusia sukarra izan ohi da, maiz sintoma bakarra ere izan daitekeelarik (ikerketa batzuen arabera, sukarra izan zen gernu kultura positiboa izan zuten bularreko haurren %78aren zeinu bakarra)[47]. Horrela, erraz uler daiteke diagnostiko zuzena egiteko zailtasuna probarik egin ezean.

Gainontzeko sintomak askotarikoak izan daitezke, suminkortasuna, gorakoak, pisu irabaztearen geldialdia, janari errefusa,… Haur jaioberrien artean, aste betetik gora irauten duen ikteriziaren arrazoi ere izan daitezke[48].

Paziente nagusiagoen artean koadro klinikoa zehatzagoa izan daiteke. Ohikoak dira disuria eta polakiuria, baina hematuria ere ager daiteke. Izan ere, gernu infekzioa da haurtzaroko hematuriaren erantzule nagusia.

Infekzioak giltzurrunean eragina duenean, sukar altuaz gain, sabeleko edo gerriko mina edota hotzikarak ager daitezke. Azterketa fisikoa egiterakoan, giltzurrun hobian egiten den kolpatzea mingarria izan ohi da, giltzurrun bueltan dagoen hanturaren adierazle.

*E. coli*a da gernu bideetako infekzioetan gehien isolatzen den bakteria; bestelako enterobakteriak, Gram negatiboak (Klebsiella eta beste batzuk) bereziki, ugariak izaten dira gernu kulturen isolamenduetan. Bularreko haur txikietan Gam positiboa den *Enterococcus*aren presentzia ohikoa izan daiteke eta aurrez osasuntsu ez diren pazienteetan bestelako bakteria eragileak aurki ditzakegu. Klasikoki, gernu infekzio larriagoekin erlazionatu izan dira nahiz eta hau zalantzan jarri azken urte hauetan[49].

Gernu bideetako infekzioaren erantzule den bakteria odol korrontera igarotzen denean, bakteriemia baten aurrean egongo gara. *Escherichia coli* da urte betetik beherako sukarra duten haurrengan gehien isolatzen den bakteria odolean eta proportzio hau are nabarmenagoa da hiru hilabetetatik behera ematen diren bakteriemietan; gernu bideetako infekzioa izan ohi dute jatorri[50].

Hala ere, eta orokorrean sukardun gernu infekzioa duten bularreko haurren artean objektibatu den bakteriemia-tasa baxua da. Gure inguruan salbuespena haurrik gazteenak dira: hilabetetik beherako haurretan %11,3ko bakteriemia tasa ikusi da, hilabete bat eta bi artean %5,9koa eta hilabete bi bete dituztenen artean %2,3ko tasa[51].

Neumonia

Munduko Osasun Erakundearen arabera, 5 urtez azpiko haurren heriotzen erantzule nagusia da neumonia; garatze bidean dauden herrialdeetan adin honetako haurren heriotzen bostena gaixotasun honek eragiten du. Herrialde garatuetan egoera erabat ezberdina da; nahiko ohikoa den diagnostikoa da baina gutxitan eragiten du ondorio larririk eta ospitalaratze tasak ez dira nabarmenegiak tratamendu anbulatorioak arrakasta izan ohi duelako[52,53,54].

Bere diagnostikorako arnas zailtasun sintomak atxikitzen dituen prozesu infekziosoak egon behar du oinarrian. Azterketa fisikoak bentilazio gutxiko birika azalera, estertore, krak edo murmurio tubarikoa bezalako zeinuak jarriko ditu agerian. Ez da diagnostikorako derrigorrezkoa irudi erradiologikoa, baina herri garatuetan ia jardun unibertsala da irudi erradiologikoak susmo diagnostikoa baieztatzea. Ohikoena, pazienteak arnas zailtasun arina izatea da.

Hala ere, kasu jakin batzuetan, oreka hemodinamikoa, kontzientzia maila… arriskuan egongo dira. Kasu hauetan, larritasuna nabarmen handiagoa izango da, sepsia definitzen dituen zantzuak bete ditzake eta egonkortze neurriak ezinbestekoak izango dira. Odolean isolamendua eman ezkero, oinarrian arnas bideetako infekzioa duen bakteriemia baten aurrean egongo ginateke.

Egia da neumonia gehienen erantzule birusak izaten direla, batik bat 5 urtetik beherako umeetan. Bakterien artean erantzule nagusia *Streptococcus pneumoniae* da edozein adinetan. Ume nagusien artean, *Mycoplasma pneumonia*ren identifikazioa ere arrunta da. Beste bakteria batzuk ere izan daitezke erantzule haur osasuntsuetan, hala nola *S. aureus*, *S. pyogenes*, *C. pneumoniae* eta b tipokoa ez den *H. influenzae*.

Aurretiaz osasuntsu ez diren umeen artean (fibrosi kistikoa edo bestelako immunogutxiegitasuna pairatzen dutenak), *Legionella*, onddo oportunistak 8candida ela Aspergillus kasu), *P. jiroveci* giza immunogutxiegitasunaren birusa (GIB), bakterio anaerobioak, … izan daitezke erantzule[54,55].

Infekzio osteoartikularra

Infekzio osteoartikularraren baitan artritis septikoa eta osteomielitisean zentratuko gara. Artritis septikoa larrialdi ortopedikoa da, gerta daitezkeen konplikazio nahiz gara ditzakeen gabezia iraunkorrak ekiditeko berehalako ekintza behar izango duena. Edozein adinetan ager daitekeen giltzadura baten edo batzuen infekzio bakterianoari deritzo, baina bi urte inguruko haurren bueltan intzidentzia handiagoa duena. Normalean giltzadura bakarrean eragiten du baina *N. gonorrhoeae* edo *N. meningitidis* erantzule diren kasuetan poliartritisak gehiagotan ageri ohi dira. Sukarra, suminkortasuna, gorputzadarra mugitu ezina, herrena…sintoma eta zeinu orokortuak izaten dira. *Staphylococcus aureus* izan ohi da bakteria erantzule nagusia, koadro sistemikoa nabarmena denean. *Salmonella* (anemia drepanozitikoa duten pazienteen artean), *S. pneumoniae*, *Streptococcus pyogenes* (barizela duela gutxi pasa dutenen artean), meningokokoa eta gonokokoa ere eragile izan ohi dira. Haur jaioberri eta gazteenen artean B taldeko estreptokokoak eta enterobakteriek ere eragin dezakete infekzioa[56].

Kingella Kingae azken urteotan infekzio osteoartikularren jatorrian lehen mailan ezarri da. Kuadro klinikoa ez da hain bat-batekoa izan ohi, sukarra ez da hain maiz egoten, pazienteen egoera orokorra ez da txarra izaten eta mugimenduen murriztapena ere ez da hain nabarmena izaten. Laborategi-teknika berriek (polimerasa kate erreakzioa oinarrian duten teknika berriek kasu) ahalbidetu dute bakteria honen eragin posible hau

detektatzea[57]; izan ere, 4 hilabete eta 4 urteko umeen artean artritis septikoaren lehen kausa da egun.

Osteomielitisa aldiz, hezurraren alde metafisarioan ezartzen den infekzioa izan ohi da, hezur muinera igaro dena, berau inbadituz. Epidemiologia eta eragileen zerrenda oso antzekoa da[56,57].

Infekzio hauen hedapena, hormaz hormako eraginaren ondorioz nahiz zuzenean odol korrontera igaro ostean gerta daiteke. Infekzio osteoartikularra eragin duen bakteria horren isolamendua odolean ere ematen denean, jatorrian infekzio osteoartikularra duen bakteriemiaz arituko gara.

Azal eta ehun bigunetako infekzioa

Bere izenak adierazten duen bezala azala eta berau osatzen duten geruza ezberdinen eta ehun, tendoi, muskulu eta abarren infekzio bakterianoak bilduko ditugu talde honetan. Euren artean, ohikoak eta larritasun gutxikoak diren inpetigoa, zelulitisa, folikulitis edo linfangitisa izan ditzakegu. Bestetik, ardura gehiago ekarri dezaketen erisipela, forunkulosia edo abzesuak izan ditzakegu. Azkenik, tratamendu oldarkorragoaren beharra izan dezaketen piomiositisa eta faszitis nekrosantea; kasu larrienetan tratamendu kirurgikoa ezinbestekoa izango da. Infekzioaren jatorria oro har, azalean sortu den garau, zauri edo lesio batek eragingo du; gutxitan izango da organismoaren beste sistema batetik hedatu izan den infekzioaren ondorio.

Erantzule nagusiak azalean bizi izan ohi diren bakteriak izango dira, *S. aureus* eta *S. pyogenes* batik bat. Egoera bereziak izango dira uretan gertatu diren zaurien kasua (*P. aeruginosa*, *A. hydrophila* eta *V. Vulnificus*), haginkadena (*P. multocida* eta anaerobioak), jaioberriena (B taldeko estreptokokoa eta Gram negatiboak), paziente inmunogutxituena

(*P. aeruginosa*, enterobakteriak eta bestelako Gram negatiboak) eta fasziti nekrosantearen kasua (*Clostridium* eta bestelako anaerobioak)[58,59].

Aparteko komentarioa merezi dute *S. aureus* eta *S. pyogenesek* sorrarazten dituzten toxinek eragiten dituzten sindromeak: azal errearen sindromea eta shock estafilokozikoa *S. aureus*aren kasuan eta shock estreptokozikoa *S. pyogenes*aren kasuan.

Azal errearen sindromean (Ritter sindromea), *S. aureus*ek azalean sorrarazi duen infekzio lokal batetik abiatuta, epidermisaren lisia eragiteko gaitasuna duten toxinak daude jatorrian. Bat-bateko sukarra, suminkortasuna eta eskarlatina itxura izan dezakeen rash mingarria izango dira sintoma adierazgarrienak. Azal erupzio hau egun bat edo bitara builaz beteko da, handik egun batzutara guztiz deskamatzeko. Shockaren kasuan toxina estafilokozikoek superantigeno modura jardungo dute. Bat-bateko sukarra, gorakoak, beherakoak, mialgiak, eritrodermia eta hipotentsioa izango dira zeinu eta sintoma nabarmenenak. Egonkortze eta mantentze tratamendua eta zain barneko antibioterapia giltzarri izango dira[60].

Shock estreptokozikoa ume gazteetan eman ohi da eta arrisku faktore nabarmenak erlazionatu dira berarekin: barizela, diabetes mellitusa pairatzea, arnas gaixotasun kronikoa, kardiopatia edo GIBa. Hilkortasun tasa handia duen gaixotasuna da, hipotentsioa, sukarra eritrodermia eta konpromezu organoanitza islatzen duten zeinu eta sintomek definituko dutena. Bere diagnosirako kriterio kliniko, mikrobiologiko eta analitikoak beharrezkoak dira[61].

Egonkor eta itxuraz ondo dauden pazienteengan burutzen diren odol hazkuntzen errendimendua oso baxua izan ohi da. Odolean isolamendu positiboa gertatzen den kasuan, jatorrian azal eta ehun bigunen infekzioa duen bakteriemiaz mintzatuko gara.

Bakteriemia ezkutua

Sukarraz gain, inolako zeinu eta sintomarik ez duen pazientearen odolean benetako bakteria baten isolamenduari deritzo bakteriemia ezkutua.

"Ezkutua" adjektiboak pazientearen egoerari egiten dio erreferentzia. Alde batetik, haurrak itxura ona izan behar du. Hau definitzeko hainbat tresna erabil daitezke. Horietako bat da ebaluazio pediatrikorako triangelua eta honen emaitza "egonkorra" hitzarekin definitzen denean, umeak itxura osasuntsua duela ondorioztatzen da[62].

Ebaluazio pediatrikorako triangelua tresna azkarra eta oso erabilgarria da paziente pediatrikoaren hasierako ebaluaziorako. Aplikazio erreza du, ez baitu estetoskopiorik, otoskopiorik edo bestelako tresnarik behar, mediku, erizain edo trebatutako teknikariaren ikusmen eta entzumenetik haratago. Tresna hau, laburbilduz, osasun-profesional bakoitzak paziente bat lehen aldiz ikusten duenean egiten duen balorazio subjektiboa egituratzen saiatzen da. Ebaluazio pediatrikorako triangelua erabiltzen den ospitale-zentro gehienetan, haren ebaluazioa triagean egiten da, zentroan zeregin horren arduradun diren langileek (mediku nahiz erizainek). Bere izenak dioen bezala, hiru aldek osatzen dute: pazientearen itxura, arnasketa lana eta larruazaleko zirkulazioa. Tresna honek ez digu pazientearen diagnostikorik ematen, baina bai egoera fisiologiko eta homeostasi egokia mantentzeko premiazko beharren berri.

Bestetik, pazienteak sukarra bai, baina sukar horren jatorria zein den adieraz dezakeen zeinu edo sintomarik ez du azaldu behar, hala nola eztula, beherakoa, amigdalen hantura, auskultazio patologikoa, polipnea, zeinu meningeoak, eta abar.

Susmopean dagoen bakteriaren arabera, bakteriemia bat izatetik meningitis bat izatera dagoen probabilitatea ezberdina da (*H. influenzae* eta meningokokoaren kasuan handiagoa da neumokokoaren kasuan baino). Behin antibiotiko dosi parenteral bakarra

jartzeak, probabilitate hori mugatu egiten du, adibidez neumokokoaren kasuan[11]. Hau da bakteriemia ezkutua bilatzeko egiten diren ahaleginen arrazoi nagusia. Aipatu bezala, kontestu epidemiologikoaren aldaketek, gizarte ohituren aldaketek, eta batik bat arrisku gehien duten pazienteen, gazteenetan oro har, zeinu eta sintomak hain inespezifikoak izateak zaildu egiten du paziente hauen identifikazioa. Saiakera handiak egin dira azken hamarkadetan, bakteriemia ezkutu bat izan dezaketen aurretiaz osasuntsu diren paziente taldeak identifikatzeko.

HAURTZAROKO IBIETAN GEHIEN INPLIKATUTAKO BAKTERIAK

Streptococcus pneumoniae

Streptococcus pneumoniae kate laburrak eratzen dituen koko Gram positiboa da. Ehun serotipo ezberdinetik gora ezagutzen dira eta bakoitza polisakarido kapsularraren arabera dago definitua. Azken honen baitan dago serotipo bakoitzaren inmunitate espezifikoa. Bakteria honek bizitzaren lehen hilabeteetan ekiten dio sudur-faringe bidearen kolonizazioari, gorengo kolonizazio maila 3 urtetara lortzen duelarik. Ordurako, haur populazioaren %25 eta %80 bitartean kolonizatuta izango da. *Streptococcus pneumoniae*k bi eratako infekzioak sor ditzake; IBIak (meningitisa, bakteriemia, sepsia, neumonia bakteriemikoa eta beste batzuk) eta ez inbaditzaileak (neumonia ez bakteriemikoa, otitisa edota sinusitisa).

Sudur-faringe bideetako kolonizazioak osatzen du *Streptococcus pneumoniae*ren gordailu bakarra eta honek errazten du bai familia artean, nahiz komunitatean eman daitekeen barreiadura[63].

Laurogeita hamarreko hamarkadaren erdian, *Streptococcus pneumoniae* zen meningitis bakterianoaren erantzule nagusia umeen artean. Azken hamarkadetan, baina, merkaturatu diren txerto konjokatuek epidemiologikoki eragin handia izan dute; erabat behera egin du bere prebalentziak garatu kontsideratzen diren herrialdeetan. Guzti honek, larrialdi zerbitzuetan burutzen ziren diagnosi eta maneiu terapeutikoen aldaketa suposatu du[64].

Neisseria meningitidis

Neisseria meningitidis Gram negatiboa den mikroorganismo diplokokoa da. Gizakia da espezie honen gordailu bakarra eta aho-sudur-faringe bidean isolatu ohi da

(garraiatzaileen portzentaiak oso aldakorrak dira). *N meningitidis, N. gonorrhoeae*rekin batera, *Neisseria* generoko espezie patogeno bakarra da.

Antigenikoki gutxienez 13 serotaldetan banatu ohi da eta *Neisseria meningitidis*aren kapsulako polisakaridoa erabili da bereizgarri. Historikoki B eta C taldeak izan dira mendebaldeko herrialdeetako gaixotasun meningokozikoak sorrarazi dituztenak, nahiz eta Y edo W135 serotaldeek erlatiboki nabarmena izan den igoera izan duten. Bestetik, epidemiak sorrarazten dituena A serotaldea izan ohi da, batik bat garatze bidean dauden herrialdeetan.

Gaixotasun meningokoziko inbaditzailearen epidemiologia, oro har, oso aldakorra da. Historian zehar uhin ezberdinak izan ditu eta datuak eskuragarri eta publiko direnetik azken hamarkadaren erdialdera argitaratu zen gaixotasunaren intzidentzia baxuena[65,66].

Izan ere, 2010eko hamarkadaren azken erdialdean nolabaiteko igoera orokor bat nabarmentzen hasi zen, ez soilik gure inguruan eta batik bat ez C eta ez B serotaldeak izanik erantzule. Aditu batzuen arabera uhin epidemiko baten aurrean egon gintezkeen, baina 2020ko Sars-Cov-2 pandemiak gogor jo eta honen aurrean ezarri ziren neurrien ondorioz (musukoa eta urruntze neurriek batez ere) Covid19 ez zen gaixotasun infekzioso transmitigarrien intzidentzia erabat apaldu zen, tartean gaixotasun meningokoziko inbaditzailearena[67,68].

*Neisseria meningitidis*ak eragindako infekzio inbaditzailearen formarik ohikoenak meningitisa, sepsia edo bien arteko konbinazioa dira. Inkubazio epea 3-4 egunekoa izan ohi da. Kalkulatzea erreza ez den arren, meningitisak sorrarazten ez duen sepsi meningokozikoak %5-20 bitartekoak dira. Sepsiak hasiera bortitza du; sukarraz gain petekia deritzen orbainak agertzen dira, denbora gutxian areagotu egiten direnak, hipotentsio, shock edo porrot organoanitzari elkartuak sarritan. Gaixotasun honen

heriotza tasak altua izaten jarraitzen du (publikazio klasikoek %10ean ezartzen dute) diagnosi nahiz tratamendu tekniken aurrerapen handia bizi izan arren; heriotz-tasa handiagoa da sepsiaren kasuan meningitis soilaren kasuan baino[30,31,46,63].

Intzidentzia gailur nabarmenenak urtebetetik beherako haurrengan, 1-4 urte bitarteko adinean eta 15-19 urte bitarteko nerabeetan eman izan dira hurrenez hurren. Urte osoan zehar gertatzen diren arren, negu eta udaberrian pilatu ohi dira, gripearen birusa agertu eta gero. Lehen ere esan dugu, baina aho-sudur-faringe bidean *Neisseria meningitidis*aren eramale diren helduak %1-15 bitartean izan daitezke eta aste edo hilabete luzeetan izan gainera. Kolonizazio honek inmunizatu gabeko haur gaztea arrisku handiko egoeretara bultza dezake.

Escherichia coli

Escherichia coli gehien ikertu den bakterioetakoa da, enterobakterioen familiako bazilo Gram negatiboa, gizakiaren kolon eta ondohesteko bakterio-floraren partaide dena eta gehienetan ez da patogenoa. Hala ere, zenbait anduik birulentzia faktoreak eskuratu dituzte eta ondorioz, gizaki eta animaliengan hainbat infekzio sor ditzakete.

Hainbat zeinu eta sintoma eman ditzakete, ondoko sindromeetan bil ditzakegunak: gernu-bideetako infekzioa, beherakoa/gastroenteritis akutua, bakteriemia eta sepsia/meningitisa.

*Escherichia Coli*a, gernubideetako mukosa kolonizatu ondoren, zelula barruan ugaritzen da, ostalariaren defentsak ekidinez. Sindrome klinikoa, batik bat gernu bideetako infekzioa, erraztuko duten hainbat birulentzia faktore izendatu dira: P eta S finbriak, hemolisina[69,70].

Beherakoa/gastroenteritis akutuaren eragile izan daitezke eta bere birulentzia markatuko duen faktore genetiko eta sorrarazitako kuadroaren arabera sailkatuko dira, patotipoak deiturikoak. Hauen artean daude, *E. coli* enteropatogenoak, enteroinbasiboak, enterotoxigenikoak… Sailkapen hau ez da lan honen helburuetako bat[71].

Oro har, esan beharrekoa da *E. coli*a 12 hilabetetik beherako haurretan *S. pneumoniae*rekin batera, odolean isolatzen den bakteria ohikoena dela[72], eta 3 hilabetetik beherakoen taldean, burua. Bakteriemia eragiten duten gernu infekzioekin batera, hau izanik diagnostiko ohikoena, bakteriemia ezkutuen eragile ere bada *E. coli*a, baina, baita haur gazteenen sepsi eta meningitisaren eragile ere[50].

Meningitisaren eragileak geruza mukosoak kolonizatu eta odol bidean inbasioa eragin duten organismoak izango dira. Meningitis bakterianoaren patogenia ostalariaren adinaren araberakoa izango da; jaioberrien kasuan, erditze bidean amaren heste edo jariakin genitalen xurgapen edo kontaktuaren ondorioz barneratu diren patogenoak izango dira hein handi baten eragile. Kasurako *E. coli*aren K1 antigeno kapsularra, B serotipodun *N. meningitidis*en kapsulako polisakaridoaren oso antzekoa da eta honek odol bidean zehar barreiatu eta hesi hemato entzefalikoa saihesteko bidea ematen dio[73].

Staphylococcus aureus

Staphylococcus aureus koko Gram positiboa da, anaerobio fakultatiboa, ohiko giza mikrobiotaren parte dena. Selektiboki koloniza ditzake sudur-zuloak, perinea, besapeak eta azal tolesdurak. Egun, aurretiaz osasuntsu diren 5 urtetik gorako paziente pediatrikoen taldean IBI gehien sortzen dituen bakterioa da eta hezur-artikulazio eta azal eta ehun bigunetako infekzioen eragile nagusia[74,75]. Gainera, shock estafilokoziko nahiz “azal errearen sindrome/Ritter sindromea”ren eragile diren toxinen erantzule ere bada *S. aureus*a.

*S. aureus*ak sortzen dituen gaixotasunak bi talde handitan banatzen dira egun: alde batetik ospitale eta osasun-zentroekin erlazionatutako gaixotasunak eta eremu hauetatik kanpo, hau da, gizarte komunitarioan ematen diren gaixotasunak.

Izan ere, ospitale eremu eta aurretiaz osasuntsu ez diren pazienteen artean, hala nola gordailu edo deribazio sistemak dituzten pazienteengan, kezka handia sortzen duen bakterioa da. Gainera, ospitalizatutako pazienteengan gertatzen diren bakteriemiak askoz ugariagoak dira fokua duten bakteriemiak baino[76]. Aurretiaz osasuntsu eta osasun zentroekin zerikusirik izan ez duten pazienteengan gertatzen diren bakteriemiek, jatorrian, hezur eta artikulazio infekzioak, ehun bigun eta larruazalekoak eta proportzio txikiagoan, neumonia izaten dute.

Ardura handia sortu duen beste ezaugarri bat, hasieran ospitalera mugatuta zegoen metizilinari erresistentea den *S. aureusa* (SAMR), handik kanpora eragiteko gaitasuna erakutsi duela da. Ikerketa asko daude abian, SAMRek komunitatean duen intzidentzia jakiteko helburuarekin. Gure inguruan burutu zen ikerketa erretrospektibo baten arabera, intzidentzia %16 inguruan dago[77].

B taldeko estreptokokoa

B taldeko estreptokokoa 3 hilabetetik beherako haurrengan diagnostikatzen diren infekzio bakteriano inbasiboen bigarren erantzule nagusia da *E. coli*aren ondoren, baina adin honetan gertatzen diren eta etiologia jakina duten sepsi eta meningitisaren eragile nagusia da [43,44,45].

Gram positiboa den koko beta-hemolitikoa da eta gaurdaino 10 serotipo identifikatu dira. Liseri hodi eta erditze kanala kolonizatu ohi ditu, behin-behinekoa nahiz iraunkorra izan daitekeelarik. Gizonezko nahiz emakumeen liseri hodia da gordailua[78].

Kolonizatuta dauden emakumeen %40-60ak transmiti diezaioke bakteria hau euren jaioberriari. Transmisio hau haurdun dagoen emakumearen kolonizazio dentsitatearekiko zuzenki proportzionala da eta antigorputz kontzentraziorekiko alderantzizkoa. Haur jaioberri hauen %1-2ak garatuko du hilkortasun eta morbilitate tasa altuak izan ditzakeen infekzioa[79,80,81,82].

Azken urteetan ezarritako estrategiek, hala nola, haurdunaldiaren azken hiruhilekoan B taldeko estreptokokoaren detekziorako egiten den screening probak eta erditzean ezarritako antibioterapia protokoloek, bakteria honek eragiten dituen infekzio goiztiarren agerpenean eragin zuzena izan du. Hala ere, ez du eragin onuragarri bera izan zazpi egunetik haratago diagnostikatzen diren infekzio inbaditzaileetan [83,84].

Honen arrazoiak bi izan daitezke: alde batetik, kolonizazioa iragankorra dela eta baheketan bakteria identifikatu ezin izatea eta bestetik, guztiz argi egon ez arren, jaioberria bera, erditu duen emakumearen liseri eta ugal aparatuko jariakinekin kontaktuan egon izana eta hauek xurgatu izana[78].

Nahiz eta adin honetan identifikatzen diren bakteriemien erantzule nagusi ez izan, kuadro kliniko larrienak sorrarazten dituen bakterioa da. Bere birulentziaren jatorria kapsulako polisakaridoak ematen dion fagozitazioa ekiditeko ahalmena da[86,87].

Streptococcus pyogenes

S. pyogenes edo A taldeko estreptokoko beta hemolitikoa deritzona, kateetan batzen den koko Gram positiboa da (A antigenoa espresatzen du pareta zelularrean eta beta hemolisia sorrarazten duten S eta O estreptolisinak dauzka). Azal eta ehun bigunen infekzioak sortzen ditu, infekzio otorrinolaringologikoak, neumonia, baina baita larriak izan daitezkeen sakoneko ehun, muskulu eta abarren infekzioak ere (faszitis nekrotizantea kasu)[58,59]. Odolean isolatzen denean, bakteriemia baten aurrean egongo gara. Paziente

pediatrikoetan bakteriemia ezkutua eragin dezake aurkezpen ohikoena ez den arren; paziente helduetan garrantzi handiagoa du[88]. Bada aurkezpen arraroagorik, hilkortasun tasa handia duena ordea, *S. pyogenes*ek sortzen dituen toxinek eragindako shock toxiko estreptokozikoa.

Haemophilus influenzae

Kokobazilo Gram negatibo hau anaerobio fakultatiboa da. Historikoki bi kategoriatan banatu da bakteria hau: kapsuladunak eta ez kapsuladunak. Kapsula da birulentzia faktore nagusiena eman izan dion ezaugarria eta B tipoko *H. influenzae* izan da historikoki, infekzio bakteriano larrienen erantzule nagusietakoa honen kontrako txerto konjokatua agertu zen arte. EEBBetan kasurako, urtean 20.000 kasu izatetik 40 kasu baino gutxiagora izatera pasa zen, 2000.urteko lehen hamarkadarako. B tipoaz gain badaude beste 5 serotipo germen kapsulatu honen baitan, goi eta behe arnas bide nahiz infekzio otorrinolaringologikoak eragiten dituztenak, batik bat. Andui hauek gehienetan patogeno oportunisten moduan jarduten dute. Ezaguna da baita ere, *S. pneumoniae* den era berean, *H. influenza*ren garraiatzaile diren 5 urtetik beherako haurren kopurua esanguratsua dela.

Egia da hala ere, XXI. mendeko bigarren hamarkadan, *H. influenzak* eragindako infekzio inbasiboek gora egiten dutela, bai serotipagarri diren nahiz serotipagarriak ez diren aldaerak (kapsularik gabekoak) daudelarik euren jatorrian[89,90].

Beste batzuk

Salmonella espeziaren kasuan, egia da *S. pneumoniae*ren azken hamarkadetako jaitsieraren ondorioz, odol laginetan agertu diren isolamenduen kopuru erlatiboak gora egin duela, batik bat paziente osasuntsuen kasuan. Hala ere, zenbaki absolutuetan ez da aldaketa esanguratsurik nabarmendu[64,91].

Gero eta garrantzi handiagoa hartzen ari den beste talde nagusia, osasuntsuak ez diren pazienteen artean ematen diren infekzio bakterioanen kasuan dauden eragileek (*P. aeroginosa* adibidez) osatzen dutena da, baita bestelako egoeretan gure mikrobiotaren parte diren bakterioak edo kasu gehienenetan kutxatutako hazkuntza balitz bezala kontsideratzen diren isolamenduak (*Staphylococcus epidermidis* eta bestelako *S. coagulasa negatibo*ak, *S. viridans* eta antzeko bakterio komentsalak, *Propionibacterium acnes*, *Corynebacterium* spp. eta bestelako *diphtheroide*ak,…) ere. Tesi honen helburua infekzio hauek ikertzea ez den arren, zenbait azalpen eta iruzkin izango dira testuan zehar.

LARRIALDI ZERBITZUKO BALIABIDEAK IBIAREN SUSMOPEAN DAGOEN PAZIENTEA EBALUATZEKO

"Zain dagoena beti zain egongo da" (BTx)

Zeinu eta sintomen multzoaren arabera, larrialdi zerbitzuan tresna eta baliabide jakin batzuk izango ditugu eskura pazientearen maneiu egokiena bilatu asmoz.

Odol, gernu eta likido zefalorrakideoan egindako testak

Odol, gernu eta likido zefalorrakideoan egin ohi diren analisiak ohikoak diren test osagarriak dira infekzio bakteriano baten susmoa azaleratzen denean eta honen jatorriaren ikerketa lanean, lehen baheketa prozesua izan ohi dira. Banan-banan aztertuko ditugu.

Odol erreaktanteak

Odoleko biomarkatzailea prozesu biologiko baten egoera normal edo patologikoaren adierazle izan daitekeen lagin biologiko batean kuantifikatu daiteken molekulari deritzo. Egoeraren monitorizazioa odolean mantentzen dituen kontzentrazioaren arabera definituko da[92].

Horregatik, odol erreaktanteek, bai klasiko eta bai modernoagoek, bere lekua dute infekzio bakteriano bat izateko susmoa duen paziente baten aurrean gaudenean, emaitzak azkar izango direlako eskuragarri. Hauen kontzentrazioen areagotzeak infekzio bakterianoekin lotu dira, era ezberdinetan, kasuan kasu. Egiten diren test guztien moduan, muga jakin batzuk dituzte; izan ere, maneiu kliniko ezberdina izango duten infekzio biralek ere aldaketak eragin ditzakete test hauetan.

Leukozito eta neutrofiloek ez dute biomarkatzailearen definizio zehatza betetzen, baina praktikan funtzio antzekoa har dezaketenez, talde honetan sartuko ditugu eta une honetatik aurrera biomarkatzaileez arituko gara.

Leukozitoen zenbaketa eta neutrofiloen zenbaki absolutua

Infekzio bakterianoa tradizionalki leukozitoen zenbaketa eta espezifikoki neutrofiloen zenbaki absolutoaren gorakadarekin lotu da. Asko ikertu da erreaktante hauen inguruan; infekzio bakteriano inbasibo edo neumokokoak eragindako ezkutuko bakteriemia izateko arrisku altuena duen pazientearen identifikaziorako erabilienak diren ebaki puntuak 15.000 leukozito eta 10.000 neutrofilo izan dira, hurrenez hurren mikrolitroko[11]. Hala ere, balio prediktibo baxua dela eta, tratamendu antibiotikoa ezartzeko erabakia datu hauetan oinarritzeak, gehiegizko tratamendua ekarriko luke berarekin[18,93,94]. Autore batzuek neutrofiloen zenbaki absolutua test zehatzagoa dela ondorioztatu duten artean, oro har antzeko profila dutela uste da[95].

C Proteina erreaktiboa

Hanturaren eraginez sortutako zitokinen areagotzearen erantzun gisa gibelak sintetizatzen duen biomarkatzailea da. Hantura agertu eta 4-6 ordura hasten da sintetizatzen gibela eta bere gorengo balioa 36 ordutara lortuko du.

Infekzio bakteriano baten diagnosiarekin lotutako ebaki puntuak ezberdinak dira adinaren arabera. Literatura zientifikoak haur jaioberrien kasuan 10-15mg/l balioak eta haur nagusiagoen artean 20 eta 40mg/l balioak onartzen ditu. Hala ere, infekzio biralek eragindako hanturak C Proteina erreaktiboaren balioak areagotzen dituela ere frogatu da.

Hainbat ikerketek prokaltzitoninaren antzeko sentsibilitatea deskribatzen dute infekzio bakterianoa identifikatzeko orduan. Hala ere, bere espezifikotasuna askoz baxuagoa da[96]. Bestetik, hainbat ikerketaren arabera, leukozitoen zenbaketa eta neutrofiloen zenbaki

absolutuarekin konparatuta, balio prediktibo altuagoa duela ondorioztatu da. Hala ere, erabakitzeko garaian hobe litzateke beste biomarkatzaile batzuekin batera konbinatzea, berak soil-soilik ez baitu ahalmen bereizlerik erakutsi[94,95].

Prokaltzitonina

Prokaltzitonina, kaltzitoninaren aitzindaria da, ohiko egoeretan tiroidearen C zelulek eta biriketako zelula neuroendotelialek kantitate txikitan sintetizatutako molekula. Hala ere, infekzio baten aurrean bere odol kontzentrazioak gora egingo du, beste hainbat ehun arduratuko baitira bere sintesiaz, hala nola, barea, testikuluak, gantz ehuna eta burmuina. C Proteina erreaktiboarekin alderatuz, odol korronteko prokaltzitoninaren kontzentrazioaren areagotzea askoz azkarragoa da.

Prokaltzitonina infekzio bakteriano inbaditzaileen identifikaziorako errendimendu handiena eskaintzen duen biomarkatzailea da urteetan zehar eginiko hainbat ikerketen arabera[27,98,99,100].

Ebaki puntuen inguruan oraindik eztabaida existitu arren, eta 2ng/ml-ko kontzentrazioa izan arren pediatrian gehien deskribatu dena, azken ikerketek 0,5ng/ml-ko kontzentrazioen alde egiten dute[98].

Gernu analisia

Gernu infekzioa prebalentzia handia daukan infekzio bakterianoa da, batik bat urte bitik beherako haurrengan[101]. Diagnosi honen susmoa, egin berri den gernu lagin baten analisi azkarrak emango digu, leukozito edo nitritoen presentziak edo Gram tindaketa batek emaitza positiboa ematen digunean. Susmoa berresteko, era esterilean hartu den gernu lagin horren kulturak bakteria baten isolamendua frogatu beharko du[102,103].

Gernu banda erreaktiboa

Erreza eta merkea den froga osagarria da, pazientearen oheburuan egin, berehalako emaitza eman eta interpretazio azkarra egiteko aukera eskaintzen duena; beraz, diagnosi eta maneiu algoritmoetan sarri aurkituko dugun testa izango da. Banda erreaktibo patologikoa (leukozituria nahiz nitrituria) urokultibo positibo batekin erkatzen dituen ikerketa ugari daude[102].

Test honek ez du berez leukozitoen presentzia esplizituki adierazten; hau da, hanturaren ondorioz leukozitoek gernuan askatzen duten esterasa identifikatzeko gai da[104]. Test honek, urokultiboa positibo izan dadin eskaintzen duen sentikortasuna %83koa da, %79ko espezifizitatea du eta %89ko balore prediktibo positiboa. Nitrituriak, aldiz, oso balio prediktibo altua dauka (%95), baina badaude nitritorik sortzeko gai ez diren eta gernu analisietan ohikoak diren bakteriak (enterokokoak, S*taphylococcus*ak eta *Pseudomona* kasu). Ikerketa ugarik konparatu dituzte sedimentua eta banda erreaktiboa, eta gernu infekzio bat izateko arriskua duten pazienteen screeningerako test egokitzat jotzen da egun, errendimendu ona ematen duelako, eta era berean oso merkea eta pazientearen oheburuan eskuragarri dagoen analisia delako[105,106].

Gainera, haurrik txikienetan nitrituriaren presentzia infekzio inbaditzaile bat izateko arrisku faktore independiente dela ere argitaratu da[107].

Likido zefalorrakideoaren analisi zitokimikoa

Likido zefalorrakideoaren (LZR) analisia meningitisaren diagnostikorako ezinbestekoa den azterketa da. Meningitis susmoa duen paziente guztietan egin beharreko analisia da, beti ere pazientearen egoerak ahalbidetuz gero.

LZR normalaren ezaugarriak ondokoak dira: koloregabea, usainik gabea eta ur distilatuaren itxura daukan arren odolaren parte diren hainbat osagai bere baitan biltzen

dituena. Bere analisi biokimikoari arreta jarriz gero, proteinak dituela ondorioztatuko da, baina plasman lortzen duen kontzentrazioarekin alderatuta, LZRan dagoena 200 aldiz txikiagoa izango da. Glukosarena aldiz, odol serumean denaren %50-75a. LZRaren leukozitoen zenbaketa ere pazientearen adinaren arabera aldatu egiten da eta eztabaidak bizirik darraien arren, onartuena ondokoa da: hilabetetik beherako haurretan pleozitosiaren ebaki puntua 20-25 zelula/mm^3, eta adin honetatik gora 10 edo 5 zelula/mm^3 izatea. Gainera leukozitoen gehiengoa linfozito edo monozitoak izango dira[108]. Beraz, ezinbestekoa izango da meningitisa izateko susmopean dagoen pazientearen maneiu terapeutikoan LZRaren ezaugarri biokimikoak aztertzea. Ezaugarri ohikoen aldaketak hanturaren adierazle izango dira. Klasikoki, ezaugarri hauen jakitun, meningitisa birala ala bakterianoa izan zitekeen susmoa nagusitu izan ohi zen. Argia ez den LZRak, neutrofiloen nagusitasuna duen pleozitosiak, glukosa kontzentrazio baxuak, hala nola proteínen kontzentrazio altuak meningitis bakteriano baten susmoan jarri gaitzake. Hala ere, desberdintasun hauek eguneroko praktikan, hain argi eta kategorikoak direnik ez da probatu[109,110]. Bestetik, aurretiaz antibiotikoa jaso duen meningitis susmoa duen pazientearen LZRak aldaketak jasan ditzake; hala nola glukosaren nolabaiteko areagotzea eta proteinen murriztea, baina ohikoa izango da leukozito eta neutrofiloen zenbakiek aldaketarik ez izatea[111].

Mikroorganismoen identifikazioa burutzeko tresnak

Infekzio bakterianoaren presentzia baieztatuko duen testik baliagarriena edozein mediotan (odol, likido zefalorrakideo, gernu edo bestelakotan) hartu den laginaren kulturan baieztatuko den mikroorganismoaren hazkuntza izan da klasikoki. Bakterioaren hazkuntzak baina, bere denbora behar du. Denbora tarte horretan paziente eta medikuak bizi duten ziurgabetasuna txikitu asmoz, erabakitzeko gaitasunean eragiten duten beste

teknika batzuk ere badira eskura larrialdi zerbitzu baten: Gram tintzio klasikoa eta azken urteotako teknologiaren garapenak ahalbidetu duten mikroorganismoen identifikazio azkarra burutzeko teknikak, polimerasa kate erreakzioa (PCR) muinean duten testak, esaterako.

Kulturak

Odol korrontea, gernua (hein handi batetan) eta likido zefalorrakideoa, berez, esterilak dira. Ondorioz, odol lagin batean benetakoa dela kontsideratzen den bakteria isolatzen denean, bakteriemia baten aurrean egongo garela definitzen da. Diagnostiko etiologikoaz gain, antimikrobianoekiko sentsibilitate testak egitea ahalbidetuko du kulturak eta baita hauen tipifikazioa ere. Kulturak, hazkuntza inguru egokiak beharko ditu, bai bakteria aerobio nahiz anaerobioentzat eta diagnosi mikrobiologikoaren urrezko patroia izango da. Hala ere, gutxieneko ugalketa denbora bat pasa beharko du hazkuntzak (24 ordu gutxienez) esanguratsu den isolamendu bat lortzeko. Horrek, larrialdi zerbitzu baten artatzen den paziente pediatrikoaren oheburuan aurrera eramaten den maneiua zaildu egiten du.

Likido zefalorrakideoaren kulturari dagokionean, berau, izango da urrezko patroia meningitis bakterianoaren diagnosian eta odol kulturen kasuen moduan, diagnostiko etiologikoaz gain, antimikrobianoekiko sentsibilitate testak eta tipifikazio testak egitea ahalbidetuko du. Likido zefalorrakideoaren prozesamenduak berehalakoa izan behar du, ordu batetik beherakoa[112]. Hala ere, 24 ordu baino gehiago behar izango du hazkuntzak germenaren ugalketa hauteman ahal izateko. Kultuaren errentagarritasuna gainera, bakterio erantzulearen eta aurretiaz antibiotikorik jaso edo jaso ezaren baitan egongo da. Neumokokoak eragindako %90ean kalkulatzen da kultura positiboa izango dela, baita meningokokoak sortutako %75ean[113]. Ikertzaile batzuek, zeftriaxonaren dosi bakarrak

(50mg/kg-ko dosia) meningokokoak eragindako meningitisaren LZRa, ordubete edo bi ordura esteriliza zezakeela ondorioztatu zuten, neumokokoak eragindakoarena 4-10 ordura eta B taldeko estreptokokoak eragindakoa 8 ordura[30,114].

Gernu infekzioari dagokiolarik, berau baieztatuko duen urrezko froga gernu kultura izango da[115]. Positibo faltsuak ekidin ahal izateko (batik bat lagina hartzeko prozeduran sortutako akatsak medio), gernu bilketak ahalik eta egokiena izan behar du: neurri higieniko egokiak hartu eta gero, bat-bateko gernua maskuri kontrola duten pazienteengan eta maskuri zundaketa edo ziztada suprapubikoa gainontzekoetan. Isolatzen den bakterio kontzentrazioak ere esanguratsua izan behar du, Ameriketako Akademia Pediatrikoaren arabera edo Espainiako Pediatria Elkarteak ezberdintasun xumeak eskaintzen dituzte[116,117].

Beste kultura batzuk ere burutuko dira larrialdi zerbitzuetan. Kasuan kasu, eta pazientearen egoeraren arabera, lagin bat edo besteren baten analisia egitea garrantzitsua izan daiteke. Hala nola, nahiz eta azal eta ehun bigunen infekzioa susmatu ezkero, draina daitekeen lesio baten kultura egitea interesgarria izan daiteke, kasu hauei atxikita dauden odol kulturen errentagarritasuna oso txikia delako, batik bat itxura onarekin eta egonkor iristen diren paziente pediatrikoetan. Draina daitezkeen lesio hauez gain, infekzio osteoartikular, isuri pleural edo bestelako jariakinen kulturak ere bere tokia izan dezake paziente baten diagnosi maneiuan (gehienetan prozedura hauek ez dira pazientea larrialdi zerbitzuan dagoela egingo).

A taldeko estreptokokoaren bilaketan, aho-faringeko kultura egokia izan daiteke; inbasibitatea eragin dezaketen liseri aparatuko infekzioetan, koprokultiboa.

Gram tintzioa

Likido zefalorrakideoan eginiko Gram tintzioak espezifikotasun handia bai, baina sentsibilitate ertaina ditu ezaugarritzat meningitis bakterianoaren diagnosian[118]. Hala ere, meningitisiaren prebalentzia baxuaren ondorioz, balio prediktibo positiboa oso eskasa da[119]. Gainera, LZRan mikroskopio bidez bakteriak ikusteko gaitasuna, bakteria beraren eta bakterioek LZRan duten kontzentrazioaren araberakoa izango da. Meningitis neumokozikoa duten pazienteen %90ak izango du Gram tintzio positiboa, %80ak meningitis meningokozikoaren kasuan, %50ak bazilo Gram negatiboen kasuan eta %33ak *Listeria monocitogenes*ak sortutakoetan[30].

Gernuaren kasuan, teknika, egin berri den gernuaren tintzio osteko mikroskopio bidezko azterketari deritzo. Espezifikotasun handiko proba da (%99tik gora), baina errekurtso handiagoak behar dituen proba izaki, ez dago beti eskuragarri eta garestia da[120]. Beraz, paziente berezi edo bereizien maneiuan baliatuko den testa izango da.

Teknika mikrobiologiko berriak

Azken urteetan teknika mikrobiologiko berriak merkaturatu dira, infekzio bakteriano nahiz biralen diagnosi eta maneiu algoritmoetan leku garrantzitsua hartu dutelarik. Polimerasan oinarritutako kate erreakzioaren teknika eta honetatik eratorritako diagnosi teknikak dira adibide ezagunena. Gainera, eratorri hauek hainbat laginetan erabili dira gaur arte: sudur eta faringe bideetako jariakinak, listuan, gorozkietan,… baina lan honetan oro har, eta bereziki puntu honetan, odol eta likido zefalorrakideoan erabiltzen den teknikaren inguruan arituko gara.

Gure inguruan, bakterien identifikaziora mugatzen diren eta odol lagina oinarri duten kit ezberdinak daude eskuragarri, meningokokoa, neumokokoa eta *Listeria* identifikatzen dituen testa delarik erabiliena infekzio bakterianoen identifikazioari dagokionean. Nerbio

sistemaren infekzioaren bilaketarako likido zefalorrakideoa helburu duten testak ere merkaturatu dira, infekzio hauen maneiuan aldaketak eragin ditzaketenak. Infekzio biralen identifikazioan ere oso erabilia da polimerasa kate erreakzioan oinarritutako testa: enterobirusak, herpervirusak, arnas sisteman eragiten duten birusak... Test hauen onurarik handiena denbora da, erabakiak hartzeko itxaronaldia askoz laburragoa den denbora tarte batera mugatzen duelako ziurgabetasuna. Hala ere, guztiak ez dira abantailak; ez daude beti eskuragarri, test bakoitzak bakteria multzo bat identifika dezake, beti dira posible positibo faltsuak eta "garestiagoak" dira momentuz.

Polimerasan oinarritutako kate-erreakzioaren teknika (PCR)

Funtsean DNA zati batetik abiatuta milioika kopia egiteko ahala duen teknika mikrobiologikoa da; genoma bakterianoaren atal jakin batzuen anplifikazioan oinarritzen da. Denbora errealean egiten den PCR bezalako teknika genomikoak praktika klinikorako diagnosi tekniken artean aurrerapen handia ekarri du.

Beste teknika batzuekin konparatuta zenbait abantaila eskaintzen ditu. Alde batetik, emaitzak denbora tarte oso laburrean daude eskuragarri. Beti ere, maneiu-algoritmo sendo eta egokien menpean, pazientearen oheburuan erabaki azkarragoak hartzeko bidea zabaltzen dute. Kit eta proba ezberdinek, sentikortasun eta espezifikotasun ezberdinak eskaintzen dituzte; kulturarekin alderatuta ordea, sentikortasuna handiagoa da teknika berri hauekin. Hala ere, momentuz ez da gomendagarria kultura, PCR teknikengatik ordezkatzea IBIen diagnosi algoritmoan[121,122].

Bestetik, esan beharrekoa da antibiotikoa lagina eskuratu aurretik ezarri izateak ez duela PCR testen identifikazio gaitasunean hain eragin bortitzik, beti ere hazkuntzarekin konparatuz. *N. meningitidis*aren identifikaziorako, PCR tekniken sentikortasuna %95 ingurukoa da likido zefalorrakideoan eskuratutako laginetarako eta zertxobait baxuagoa

odol laginetarako. DNA meningokozikoa antibioterapia sistemikoa hasi eta 72 ordura arte antzeman daitekeen arren, kontu handia izan behar da teknika honen bitartez ondorioztatutako emaitza negatiboak interpretatzerako orduan, gaixotasunaren aurkezpen klinikoak, larritasunak, iraupenak eta tratamendu antibiotikoaren hasiera uneak bere eragina izan dezaketelako testaren errendimenduan [3,123,124].

Azken aldian teknika honetan oinarritutako beste aukera batzuk merkaturatu dira: mikroorganismo ugari biltzen dituzten panelak, FilmArray panel multipleak kasu, zenbait algoritmotan ohorezko lekua har dezaketenak. Ohiko denbora errealean irakurtzen diren antzeko testekin konparatuta, anplifikazioa eta irakurketa ez dira aldi berean burutzen eta honek agente infekziosoaren material genetikoaren presentziaren edo gabeziaren interpretazio kualitatiboa baino ezin egitea dakar. Abantaila ikaragarriak izan ditzakeen arren (emaitzak ordubetearen buruan izan ditzakegu adibidez *FilmArray® Panel meningitis-encefalitis* testaren kasuan), test honek ere bere mugak ditu: lortutako emaitzak kualitatiboak dira; panelak eskaintzen dituen mikroorganismo zerrendaren presentzia baino ez du ondorioztatzen; lan-eremu homogeneo batetik kanpoko emaitzek, ondo aztertutako lan-algoritmo hertsietatik kanpora lortutakoek, interpretazio zailak izan ditzakete (herpes birus familiaren presentziaren interpretazioa esaterako, giza-genoman integratzeko duen gaitasuna medio).

Irudi-teknikak

Zenbait irudi-teknika baliagarri eta osagarri izan daitezke larrialdi zerbitzuan sukarra duen paziente bat artatzen ari garenean. Esaterako, infekzio osteoartikularraren susmopean dagoen pazientearen aurrean, gidek gomendatzen duten lehen irudi-froga erradiografia izaten da[75,125].

Hala ere, gure inguruan kontsultatzen diren infekzio osteoartikularren susmopean dauden kuadro klinikoak larregi eboluzionatu gabeko kuadroak izan ohi dira eta normalena litzateke esanguratsu diren ezaugarri erradiologikoak oraindik ageriko ez izatea eta test honek maneiu terapeutikoan erabakien aldaketarik ez sortaraztea. Ekografia muskuloeskeletikoak, artritisaren susmopean dauden kuadro klinikoetan bere lekua izan dezake, artikulazioan likidorik dagoen edo ez ondorioztatzeko eta drainatze tekniketan lagungarri izateko[126].

Arnas zailtasuna ageri duten sukardun pazienteengan neumonia izan daiteke diagnostikoetako bat. Gida gehienek ez dute erabat derrigorrezkotzat jotzen irudi erradiologikoaren beharra paziente jakin bati neumonia diagnostikoa ezartzeko, nahiz eta ohiko praktika izan herrialde garatuetan eta batik bat errekurtso hori gau eta egun eskuragarri dagoen zentroetan. Badaude egon, hala ere, erradiografia egitera bultzatuko gaituzten indikazio jakinak[55,127]. Azken urteetan, halaber, leku handia hartu du pazientearen oheburuan egiten den birika ekografiak, erradiologoa ez den medikuak egiten duena eta emaitza onargarriak izaten ari dena. Hala ere, oraindik ebidentzien babesa ez da erabatekoa; bere mugen artean, profesionalen arteko aldakortasuna da garrantzitsuena eta esperientziak garrantzi handia izango du[128].

Protokoloak

Protokoloak edozein sistemak segurtasunez funtzionatzeko beharrezko dituen tresnak dira. Larrialdi zerbitzu pediatriko bati gagozkiolarik, ebidentzia zientifikoan oinarritutako maneiuak izan behar dute eta tokian tokiko errekurtsoetara moldatuta egotea.

Kuadro kliniko ezberdinen aurrean prestatuta ditugun protokoloek, profesional bakoitzak antzeko kuadroaren aurrean egiten duen maneiu terapeutikoan aldakortasuna murriztea

ekarriko du; sistema eta pazientearen onura klinikoa, ekonomikoa eta segurtasuna, hein handi batean bermatuko du.

Hurrengo puntuetan maneiu ezberdinen azalpenaz arduratuko gara.

Aurrez osasuntsuak ez diren pazienteak

Gero eta ohikoagoa da larrialdi zerbitzu baten aurretik osasuntsu ez diren pazienteak artatzea. Paziente kronikoen bizi kalitate eta esperantzak gora egin du azken hamarkadetan. Ebidentzia zientifikoak aurrera egin ahala, erakunde ezberdinek infekzio bakteriano larri bat izateko arrisku gehiago duten pazienteen diagnosi eta tratamendu algoritmoetan moldaketak egin dituzte.

Askotariko dispositiboen garraiatzaile diren pazienteen, hala nola deribazio bentrikulu peritoneal edo antzekoak diren balbula, kateter zentral edo erreserborioa, edo hemodialiasia egiteko beharrezko diren dispositiboak dituztenetan, hurbilketa diagnostikoak ezberdina izan behar du. Azken urteotan paziente onkologiko edo bestelako immunogutxituen prozedurak ere aldatuz joan dira, bestelako paziente kronikoen ikuspuntuak indibidualizatu egin dira, gernu bideetan malformazio garrantzitsuak dituzten paziente pediatrikoen lehentasunak finkatu dira, eta abar luze bat. Tesi honen helburua ez da arrisku-talde bakoitzaren protokoloak banan-banan azaltzea; gainera, tesi honen hasiera markatzen duen artikulutik azkenengora, protokolo ezberdinek aldaerak izan dituzte eta maneiu pertsonalizatuak ere jaso izan dituzte pazienteek kasuan kasu.

Aurrez osasuntsu diren pazienteak

Gainontzeko pazienteak aurrez osasuntsu diren paziente definituko ditugu. Hauek, oro har, infekzio larriagoak pairatzeko arrisku gutxiago izango dute. Horregatik, paziente

hauenganako hurbilketak ere garrantzi handia izango du, pazientearen segurtasunean eta sor daitekeen iatrogenian ere eragina izango duelako.

Sukarra daukan paziente baten edo infekzio baten susmopean dagoen paziente baten aurrean, medikuak eman behar izaten duen pausurik baliozkoena, paziente horrek tratamenduren bat lehen bait lehen jaso behar duen edo ez erabakitzea da; hau da, larri dagoen edo ez; egonkor dagoen edo ez ebaluatzea. Horretarako hainbat eskala eta erabaki tresna erabiltzen dira, aurrez komentatu den ebaluazio pediatrikorako triangelua deritzona kasurako[62]. Sukarra dela eta artatzen diren pazienteen gehiengoa egonkor heltzen da larrialdi zerbitzura. Behin egonkortasuna bideratuta, hurrengo erabaki garrantzitsua fokurik gabeko sukar eta fokudun sukarraren arteko ezberdintasuna egitea izango da.

Sukar horren jatorria azal dezakeen anamnesi eta azterketa fisikoak, froga osagarriak egitera edo ez egitera eramango dute medikua, batik bat tratamendu antibiotikoa behar duen ala ez erabakitzeko. Goi arnas bideetako infekzio baten kasuan, azterketa fisikoak bentilazio gutxiko birika eremu bat azaleratuz gero, neumonia baten zantzuak hauteman ditzake eta kasuan kasu erabakiko du irudi probaren bat egin behar duen edo ez, tratamenduarekin hasteko. Bestetik, azterketa fisikoak zantzurik eman ezean, gomendio ohikoena tratamendu sintomatikoarekin aurrera jarraitzea izan ohi da[55,127], nahiz eta jakin, paziente multzo honen barruan IBI bat paira dezaketenak egon daitezkeela.

Gernu-bideekin erlazionatutako sintomak gehitzen bazaizkio sukarrari, gernu-bideetako infekzioa ondorioztatu dezaketen frogak egingo dira; gernu banda erreaktibo eta kultiboa, berau normala izan ezean. Azal eta ehun bigun edo infekzio osteoartikular edo infekzio otorrinolaringologikoen kasuan, azterketa fisikoak informazio handia emango du froga osagarriak egin behar diren edo ez erabakitzeko, eta kasuan kasu, tratamendu antibiotiko anbulatorioa edo zain-barnekoa ezatzeko.

Meningitisa susmatzen den kasuetan, gerta daiteke pazienteak ebaluazio pediatrikorako triangelu egonkorra izatea, ohikoena izan ez arren. Helburu nagusia, meningitisa pairatzen duen haurraren identifikazioa da eta hurrengoa meningitisaren jatorria birala edo bakterianoa den ondorioztatzea. Meningitis bakteriano baten aurrean antibiotikoaren administrazio goiztiarrak pronostikoaren hobekuntza dakar. Bestetik, birala den meningitisa identifikatzeak, alferrikakoak diren tratamendu eta ospitalizazio egonaldiak ekidingo ditu, sorrarazten duen iatrogeniarekin batera. Hala ere, identifikazio hau ez da batere erraza, zeinu patognomonikorik ez izateak eta pazienteen kontsulta goiztiarrak, zeinu eta sintomen inespezifikotasuna baitarama berarekin. Likido zefalorrakideoaren analisi eta kulturak emango dute diagnostikoa, hau da giltza. Hala ere, kulturaren emaitza ez da berehalakoa eta azken urteetan hainbat saiakera egin dira diagnosi prozesu honen zehaztasuna areagotzeko, hainbat *score edo aurreikuspen klinikorako tresna* eta gida publikatu baitira ziurgabetasun hau murrizte asmoz[129,130]. *Scor*e hauek datu kliniko eta analitikoak (odol eta likido zefalorrakideoan) uztartzen dituzte.

Azkenik, teknika mikrobiologikoen agerpenak eta PCR tekniken agerpenak batik bat, diagnosi algoritmoetan erabaki goiztiarragoak hartzeko aukera erraztu dute.

Tesiaren sarreran aipatu bezala, larritasun gehien sorrarazten duten infekzio bakterianoak odol edo LZRan isolatzen diren bakteriek eragindakoak dira. Infekzio bakteriano inbasibo larriena ez den arren, bakteriemia ezkutua, hauen adibidetako bat da. Ebaluazio pediatrikorako triangelu egonkorra duen sukardun paziente baten odolean bakteria bat isolatzen denean definitzen den egoera da, non azterketa fisiko nahiz gaixoaren sintomek sukar honen jatorria zein den azal ezin dezaketenean.

Bakteriemia ezkutuaren bilaketa aktiboan ahalegin oso biziak egin diren paziente multzo bat, aurretiaz osasuntsuak diren 0-3 hilabeteko haurren taldea da. Adin honetan, *E. coli*

eta B taldeko estreptokokoa dira eragile ohikoenak. Immunitate sistema heldugabeak eta txertaketa programa hasi gabe egoteak ere, beste arrazoi batzuen artean, infekzio bakteriano larri bat izateko hautagai egiten dituzte. Hala ere, haur hauetako asko ingresu eta antibiotikorik gabeko jarraipena izateko hautagaiak dira gaur egun. Asko izan dira saiakerak, Rochesterren irizpideetatik hasi eta gaurdaino (Philadelphia eta Boston irizpideak), baina lortu diren atxikimendu tasak ez dira nabarmenegiak izan[131]. Azken urteetan agertu diren biomarkatzaile berriek eta urteetan zehar burututako lanaren emaitzek, bularreko haur txikien maneiu berri bat erraztu dute. Gure inguruan, "Step by Step" eta PECARN gida dira paziente hauen maneiuan gehien erabiltzen diren tresnak[132,133,134]. Hala ere, tresna hauek ez dira finkoak diren estrategiak eta denborarekin eta agertzen ari den ebidentziekin aldaketa nabariak bizi izan dituzte.

Nagusiago diren haurretan, batik bat, aurretiaz osasuntsuak diren 3-24 hilabeteko sukarrarekin dauden paziente multzoa da asko ikertu den beste talde bat. Historikoki, talde honetan *S. pneumoniae* zen gehien isolatzen zen bakteria baina *Haemophilus influenzae*ren bakteriemia ezkutuak eragiten zituen konplikazioak, meningitisa, ondorio larriak eta heriotza tasa latzak ziren[135]. *Haemophilus influenzae*ren kontrako txertoak unibertsalizatu zirenetik, bakteriemia ezkutuaren tasak behera egin zuen nabarmen[136]. Azken urteetan hedatu diren neumokokoaren aurkako txerto konjokatuek ere infekzio inbasibo neumokozikoen jaitsiera nabarmena ekarri zuten. Txerto zazpibalenteak batik bat bakteriemia ezkutu neumokozikoaren jaitsiera nabarmen bat ekarri zuen berarekin[3,7,8]. Joera honek 2010 urtean zabaldu zen txerto konjokatu hamahirubalentearekin berdintsu jarraitu zuen eta serie batzuen arabera, neumokokoa ez litzatekeen gehien isolatuko zen bakteria izango [64,137,138].

Leeren artikulu klasikoaren arabera, bakteriemien tasa %1,5etik gorakoa denean justifikatua dago eta koste-eraginkorra da gainera, jatorri argirik gabeko sukarra duen haur batengan bakteriemia ezkutu baten zantzuak adieraz ditzakeen odol testak egitea eta emaitzen baitan antibiotikoa jartzea [5,11]. Aitzitik, tasa %0,5etik behera dagoenean, ez dago gomendiorik testik egiteko.

Baina gure inguruan bakteriemia ezkutu neumokozikoaren prebalentzia oso baxua da eta hainbat gidek ez dute gomendatzen gaur egun odol analisirik egitea ondo txertatuta (neumokokoaren aurkako txerto konjokatuaren dosi bi gutxienez jasoak izatea), aurretik osasuntsu eta egonkor dauden 3-24 hileko sukarra duen haurra ebaluatzerakoan[139]. Izan ere, gaur eguneko ikerketen arabera, bakteriemia ezkutuaren tasa oso baxua da egoki txertaturiko populazioan[140].

Sepsi baten aurrean egon gaitezkeela ondorioztatuz gero, pazientearen egonkortze prozeduran eragin dezaketen tresna guztiak jarriko dira martxan. Orokorrean, ebaluazio pediatrikorako triangelua ez da egonkorra izango, monitorizazioa ezinbestekoa izango da eta arnas bidea mantentzeko bermea eta oxigenazio eta bentilazio egokiena lortzeko eskura dauden baliabideak jarriko dira martxan, oxigenoterapia, nahiz bentilatzea posible egiten duten bestelako terapiak, inbasiboa nahiz ez inbasiboak. Organoen perfusioa mantentzeko ezinbestekoak diren zainbideak lortuko dira eta gutxieneko tentsioa lortzeko sueroterapia eta droga basoaktiboen terapiei emango zaie lehentasuna. Antibiotikoa espektro zabalekoa izango da eta sepsiaren kasuan lehen hiru orduetan ezartzea gomendatzen dute gida berrienek, lehen orduan shock septikoaren kasuan.

AZKEN HAMARKADETAKO ALDAKETAK

"Gogoratzen zara norabidea alda arazi zizun berriaz?" (BTx)

Biztanlerian gertatutako gizarte aldaketak

Mendebaldeko gizarteek azken hamarkadetan izandako aldaketa soziokulturalek (seme-alaba gutxiago, emakumeak lan-merkatuan sartzea, informaziorako sarbide handiagoa eta errazagoa) eragin argia izan dute haiek eskaintzen dituzten osasun zerbitzuetan. Modu honetan, sukarra duen umearen kasuan, familiak maizago eta, batez ere, azkarrago joaten dira medikuarengana, ohiko medikuarengana edo eskuragarri dagoen eta konfiantza sortzen duen beste batengana; askotan, zentro hauek ospitaleetako larrialdietako zerbitzuak dira[141]. Horrela, gaur egungo mendebaldeko gizarteetan, euskal gizartea barne, sukarra da ospitaleko pediatriako larrialdi zerbitzuetan kontsultatzeko arrazoirik ohikoenetako bat. Gainera, gure ingurunean ere hala da, familiek goizago kontsultatu ohi dute. Azken urteotan, larrialdi zerbitzuek erregistratutako kontsulten gorakada nabarmena bizi izan dute[142,143]. Fenomeno hau mendebaldeko hainbat gizartetan salatu izan da, baita Euskal Herrian ere[141].

Larrialdi zerbitzuetako kontsulten gorakada honen ondorio, zerbitzu horiek beren baliabideak egungo eskarira egokitzera eraman dituzte, baliabide, arkitektura, pertsonala eta antolaketaren ikuspuntutik. Hala ere, askotan zerbitzu hauek saturaziotik hurbil dauden egoerak jasaten dituzte eta horietan lan egiten duten profesionalen lana oztopatu egiten dute[144,145].

Beste alde batetik, jakina da gure inguruan kuadro klinikoen eboluzio denborak ez direla oso luzeak izaten. Kasurako, fokorik gabe sukarrarekin kontsultatzen duten 3 hilabetetik beherako haurren sukarraren iraupenaren mediana bi ordutakoa izan zen azken bost

urteak bildu zituen ikerketaren lagin honetan[146]. Horrek zaildu egiten du IBIa duen pazientea identifikatzea, azterketa fisikoak zein proba osagarriak egiteak dituzten mugak direla eta.

Osasun arloko aldaketak

Azken hamarkadetan osasun arloan eta baita gainontzeko edozein arlotan ere, teknologiaren bidetik batik bat, aurrerapen garrantzitsuak izan dira. Aldaketa guzti hauek bere eragina izan eta izango dute larrialdi zerbitzuan artatuko ditugun sukardun paziente eta haien senideekin elkarlanean burutuko dugun kudeaketan.

Jaio aurreko ekografia

Jaio aurreko ekografiaren unibertsalizazioak jaioberri batek izan ditzakeen malformazio garrantzitsu askoren jaio aurreko diagnostikoa erraztu du.

Gehien aurkitzen diren anomaliak giltzurrunarekin eta gernu-aparatuarekin lotutakoak dira[147,148]. Horien artean, gehien aurkitzen den anomalia hidronefrosia da, %0,5-1eko intzidentziarekin[149,150]. Jaio aurreko hidronefrosia antzematen den haur guztiek gerora gernu-bideekin erlazionatutako patologiarik jasango ez duten arren, paziente talde honen ehuneko esanguratsu batek ureter eta pelbisaren arteko lotunean oztopo-maila ezberdina eragin diezaioken lesioa izan dezake[151] eta, beste autore batzuen arabera, paziente multzo honen %35ak errefluxu besikoureterala izan dezakete[152]. Klasikoki, malformazio nabarmenenak jaioberriaren ohiko lehen azterketan susma zitezkeen, batik bat giltzurrunaren palpazioa eginez gero giltzurrun-gutxiegitasunetik eratorritako zeinu eta sintomen harira. Baina kasu gehienetan, diagnostikoa fokurik gabeko sukarrarekin kontsultatzen zuen haurrak gernu-infekzioa pairatu eta haren azterketa egitean azaleratzen zen. Gaur egun, jaio aurreko ekografiari esker, gernu infekzio bat izateko arriskua duen haur taldea aldez aurretik identifikatzeko gaitasuna du pediatrak.

Horregatik, kasu hauetan paziente horrengana egiten den hurbilketa prozesua ezberdina izango da.

B taldeko estreptokokoaren detekzioa haurdun dauden emakumeengan

B taldeko estreptokokoa edo *Streptococcus agalactiae* jaioberrien sepsiaren eta meningitisaren kausa nagusitzat aitortu zen 1970eko hamarkadan[153].

Aurrerago, beste autore batzuek meningitisarekin (%39), bestelako infekzio fokalekin (%10) eta sepsiarekin (%7) erkatu dute, tasa oso nabarmenekin[154]. Azken urteotan, erditze barruko antibiotiko profilaxiaren erabilerak germen honen infekzioen intzidentzia murriztu du[155,156,157].

Profilaxi honek infekzio goiztiarrak murrizten ditu batez ere, infekzio berantiarren murrizketa paralelorik ez delarik deskribatu[158,159,160].

Ikerketa batzuen arabera, Ameriketako Estatu Batuetako B taldeko estreptokokoaren gaixotasunaren intzidentzia gutxitu egin da, 1990ean 1.000 jaiotzako 1,8 kasutik 2003an 1.000 jaiotzako gertatu diren 0,32 kasura[161,162]. B taldeko estreptokokoek eragindako gaixotasun goiztiarraren heriotza tasa globala aldiz, 70eko hamarkadan erregistratzen zen %50etik, 1993-2003 hamarkada artean antzeman zen %5-6ra igaro da, jaioberriari eskaintzen zaizkion arreta mekanismo eta zainketei esker batik bat[160,163]. Emakumeen haurdunaldiaren hirugarren hiruhilekoan egiten den bakterioaren bilaketa sistematikoak eta emaitza honen arabera hartzen diren erabakiek (erditze lanetan ezartzen den tratamendu antibiotikoa) B taldeko estreptokokoak kutsatutako jaioberrien intzidentzia murriztu du[164,165]. Azken urteetan, esan dezakegu bakteria hau ez dela fokurik gabeko sukarra duten 3 hilabetetik beherako pazienteen infekzio inbaditzaileetan isolatzen den bakteriarik ohikoena gure ingurunean[23,166]. Etorkizunari begira, B taldeko estreptokokoaren kontrako txertoetan esperantza handia jarrita dago.

Txertaketa egutegia

Mundu mailan, ura edangarri egiteko prozedura eta gero, infekzio arriskua historikoki gehien jaitsi duen aurrerakuntza txertaketa egutegiaren ezarpena izan da.

Txertaketa sistematikoak infekzio larriak jasateko probabilitatea asko jaisten du. Azken urteetako txertaketa kanpainek, sepsi eta meningitisen eta ondorioz heriotza eta luzerako albo kalteen murriztapena ekarri dute. Tesi honen kapitulu honetan, *Haemophilus influenza*e, meningokoko eta neumokokoaren aurkako txerto konjokatuetan zentratuko gara, hauek direlako gure inguruko IBIetan eraginik handiena izan duten txertoak.

*Haemophilus influenzae B*ren aurkako txertoa

H. influenzae B motako txerto unibertsalak ia guztiz ezabatu ditu bakterio honek eragindako gaixotasun inbaditzaileak[167]. Izan ere, gaur egun salbuespena da behar bezala txertatutako ume batek *Haemophilus influenzae B* motako infekzio inbaditzaile bat pairatzea[168]. Txerto aurreko aroan, B motako *H. influenzae*k eragindako infekzio inbaditzaileen kasuen gehiengo zabala (%80tik gora) bost urtetik beherako haurretan detektatzen zen, eta batik bat urte bitik beherakoetan[167]. Bakteriemia ezkutuen arduradun nagusietako bat izan zen bakteria hau, baina baita konplikazio gehienen eragile ere. Izan ere, bakteriemia horien %10-20 inguruk, meningitisa eragiten zuten gerora[169]. Txerto honen unibertsalizazioak eragindako zuzeneko eta zeharkako babesa dela eta, ia gaixotasunaren erabateko gutxitzea eragin zuen eta fokurik gabeko sukarrarekin artatzen zen haurraren kudeaketa eraldatu [170,171,172,173,174,175].

*Neisseria meningitidisar*en aurkako txertoak

Meningokokoa uhin epidemikoak sorrarazten dituen bakteria da. 1980-1990 hamarkadan gaixotasun meningokozikoen gorakada nabarmena izan zen. Egia da, neurri batean

PCRan oinarriturako diagnostiko-tekniken hobekuntza medio azal daitekeela igoera hau[176,177].

Edonola ere, urte haietan C serotaldedun gaixotasun meningokokoaren kasuak neurrigabe handitu ziren Europako hainbat herrialdetan, Ingalaterran eta Galesen[178,179], Grezian[180] edo Espainian[181] kasu. Igoera hori Kanadan ere jakinarazi zen[182]. Igoera hori garrantzitsuagoa izan zen bi adin-taldetan, 2 urtetik beherakoetan eta 15 eta 19 urte bitartekoetan. *H. influenzae B*-k eragindako gaixotasun inbaditzaileek jaso zuten beherakada C meningokokoari ere aplikagarria da txertaketa programetan C meningokokoaren txerto espezifikoa gehitzeari esker[183]. Izan ere, C serotaldeak sorrarazitako kasuen gutxiagotze honen arrazoia 2000. urtean hasitako txertaketa kanpainan aurki daiteke. Txerto honen eraginkortasuna urtez urte egiaztatu da. Hala, C serotaldeak eragindako infekzio inbaditzaileen intzidentziak erabat egin zuen behera, 0,04 kasu/100.000 biztanleko 2014-2015 denboraldian[184,185].

Hala eta guztiz, gure inguruan eta serotalde guztiak aintzat hartuta, B serotaldea izan da guztietan prebalenteena, 90. hamarkadako uhin garrantzitsu hori albo batera utzi badaiteke. *Neisseria meningitidis*ak, bestetik, bere aldaera guztiekin eragindako infekzioen intzidentziak beheranzko joera izan du Espainiar estatuan 2000. urtetik hona. Baieztatutako kasuen intzidentzia tasarik baxuena 2013-2014 denboraldian eman zen, 0,5 kasu ingurukoa 100.000 biztanleko. Hala ere, kasuen erdiak baino gehiago, B serotaldeak eragindakoak izaten jarraitu zuten. Joera hau orain hamarkada bi hasitakoa dela ere bada aipatzekoa. Jaitsiera honen arrazoia, gaixotasunak berak eskaintzen dituen aldian aldiko patroiaren baitan egon daiteke, B serotaldearen txerto konjokatu berriak ezin izan duelako momentuz hain eragin esanguratsurik izan; 2015eko urrian hasi zen komertzializazioa eta

gainera, autonomi erkidego batzuren txertaketa kanpainen parte baino ez da oraingoz[65,185].

Bi mila eta hamabost urtetik aurrera, zifrak zertxobait gora egin zuen, intzidentzia tasa 0,83[67] kasutara iritsi zelarik, batik bat W135 serotaldearen areagotzearen ondorioz. Hainbat aditu meningokokoaren uhin epidemiko berri baten aurrean geundela esatera ere iritsi zen.

<u>*Streptococcus pneumoniae*ren aurkako txertoak</u>

Hogeitahiru serotiporen babesa eskaintzen zuen txertoa 1977 urteaz geroztik eskuragarri bazegoen ere, ez zen oso eraginkorra 2 urterik beherako haurren artean, sistema immunitarioak adin honetan eskaintzen duen heldutasun falta dela eta.

Bi milagarren urtean, *S. pneumoniae*ren zazpi aldaeren polisakaridoz eratutako (4, 6B, 9V, 14, 18C, 19F y 23F) txerto konjokatu heptabalentea onartu zen (PCV7). Lehendabizi Estatu Batuetan eta gerora, Europar Batasuneko immunizazio programei atxikitu zitzaien. Txerto honek, neumokokoaren eraginez 2000.urtean Estatu Batuetan antzeman ziren infekzio inbaditzaileen %80tik gorako estaldura eskainiko zukeen[33,186,187]. Txerto honen komertzializaziotik hona, *Streptococcus pneumoniae*k eragindako infekzio inbaditzaileen intzidentzia orokorrak nabarmen egin du behera adin talde guztietan, baina batik bat urte bitik beherako haurrengan, txertatuta egon edo ez[31,183,188].

Bestetik, PCV7 bidez eginiko txertaketa ia unibertsala bizi izan zen arren, ikerketa berri eta zenbait zaintza eta begirale-sareren informeek, txertoek eskaintzen zuten estalduraz kanpoko serotipoek eragindako infekzioen gorakada jaso zuten: batik bat, 1, 19A, 7F, 3 eta 6Ak eragindakoak, “serotipoen ordezkapena” bezala deitua. Hemeretzi A serotipoa gainera, multierresistentzia antimikrobianoen %80a bere baitan soilik biltzeko gai izan dena, txerto konjokatu zazpibalentearen sarreraz geroztiko infekzio inbaditzaileen kausa

garrantzitsu bihurtu zen[6,183,188,189]. 2010ean, txerto konjokatu hamahirubalenteak zazpibalentea ordezkatu zuen, Estatu Batuetako txertaketa programetan. Txerto honek, aurreko urteetan jazo zen "serotipoen ordezkapena" eragin zuten aldaerak bildu zituen, tartean 19A eta 7F. Gaixotasunen kontrol eta prebentziorako zentroaren (CDC) argitalpen eguneratu baten[190] txerto aldaketa honek 5 urtetik beherako umeengan *Streptococcus pneumoniae*k eragindako infekzio inbaditzaileen %64ko murrizketa eta txerto 13balenteren barnean dauden serotipo berriek eragindako infekzio inbaditzaileen %93ko murrizketa eragin duela publikatu zuen[191,192,193,194]. Bost eta 15 urte bitarteko pazienteengan txerto 13balentean integratutako serotipoen ondorioz jazotako infekzio inbaditzaileen intzidentziak %75 egin zuen behera. Oro har, adin talde guztietan izan zuen ondorio bera, batik bat 19A eta 7F serotipoen gainbehera zela eta[194,195]. Guzti honek eragina izan du sukarrarekin datorren bularreko haur baten kudeaketa egiterakoan. Egun, IBI neumokozikoen parte handi baten erantzule diren bi serotipo "berri", etorkizun hurbilekoko txertaketa egutegietan sartzear daude[196]. Honek ere azpimarra egiten du IBIen monitorizazioa egiteko beharraren garrantziaz.

LAN HIPOTESIA

Arkatzekin armatuta arriskutsuak gara,
hondarrezkoak direnez zuen gaztelu gotorrak
ideien olatu honek botako ditu (BTx)

LAN HIPOTESIA

Egun, IBIa duen pazientea, oso goiz iritsi ohi da larrialdi zerbitzuetara, sintomak eta azterketa fisikoan ager daitezkeen zeinuak inespezifikoak direnean. Paziente horien gehiengoa oso gaztea da eta horrek infekzio desberdinen karakterizazio klasikoa kasu bakanetan agertzea ondorioztatuko du. Azken urteotan ezarri diren txertaketa kanpaina ezberdinek IBIen ezaugarri epidemiologikoak aldatu dituzte. Honek guztiak medikuaren erabakitzeko gaitasunean bere eragina izan du.

Aitzitik, IBI bat izateko arrisku handiagoa duten sukardun pazientea identifikatzeko jardunean, odol analisiaren munduan nahiz bestelako baliabideetan egindako aurrerakuntzek, sukarra dela eta larrialdi zerbitzura datorren pazienteengan egin daitezkeen proben kopurua handitu egin da. Ezaugarri askok izango dute eragina froga hauen errendimenduan; are gehiago, froga hauek egingo diren pazienteak ondo sailkatu ezean.

Finean, IBIak arazo larria izaten jarraitzen dute. Azken urteotako aldaketen harira, IBIen zenbaketa globalak behera egin du batetik, eta bestetik, osasun zerbitzuan egiten diren kontsultak askoz goiztiarragoak dira. Medikuaren erronka nagusi bat, egonkor azaldu eta sukarra duen pazienteak IBIa izan dezakeen identifikatzea izango da, anamnesi, azterketa fisiko, eta beharrezko ikusten duenean, beste test eta froga ezberdinez baliatuta.

Gure hipotesi nagusia hauxe da: IBIa pairatzen duen pazienteren karakterizazioak eta hauen identifikaziorako ditugun baliabideen errendimenduak aldaketak jasan izan ditzake azken urteotan. Baliabide multzo honetan anamnesia, azterketa fisikoa eta larrialdi zerbitzu batean egin ditzakegun froga osagarriak bilduko ditugu.

HELBURU NAGUSIAK

1. Hamalau urtetik beherako pazienteetan baieztatu diren IBIen aurkezpen klinikoaren karakterizazioa deskribatu.
2. Hamalau urtetik beherako pazienteen IBIen larritasuna deskribatu.
3. Hamalau urtetik beherako pazienteen IBIak identifikatzeko egiten diren ohiko odol testen (leukozitoen zenbaketa, neutrofiloen zenbaki absolutua, proteina C erreaktiboa eta prokaltzitonina) balioa analizatu.
4. Fokurik gabeko sukarra duten eta larrialdi zerbitzura egonkor iristen diren 3-24 hilabete arteko haurrak artatzerakoan odol testik ez erabiltzearen gomendioa ebaluatu.
5. *E. coli*k eragindako infekzio inbaditzaileen aurkezpena deskribatu eta balizko profilak eta larritasunarekiko balizko harremana ikertu.
6. B taldeko estreptokokoak eragindako infekzio inbaditzailearen aurkezpena deskribatu eta haren larritasunarekiko balizko harremana ikertu.

BIGARREN MAILAKO HELBURUAK

Tesi honen helburu ez zen arren, aurretik espero ez genuen pandemia batek larrialdi zerbitzu baten identifikatu diren IBIen epidemiologian izan duen eragina deskribatu.

METODOA

Nola azalera irten? (BTx)

METODOA

ARGITARATUTAKO ARTIKULUAK ETA KALITATEZKO INDIZEAK

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Characteristics of children with microbiologically confirmed invasive bacterial infections in the emergency department

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Background **Determination of the characteristics of paediatric invasive bacterial infections (IBI) is essential for early identification of children requiring immediate antibiotic therapy. The main objective is to characterize the emergency presentation of the IBI among children aged younger than 14 years.**

Patients and methods **A prospective registry-based cohort study including all patients aged younger than 14 years diagnosed with confirmed IBI (culture or genomic detection using the polymerase chain reaction) was carried out in a paediatric emergency department between 2008 and 2015. Severity criteria were as follows: death, sequelae or admission to the ICU.**

Results **Of the 223 IBIs reported, 187 (83.9%) corresponded to previously healthy patients (median age = 19 months) and 165 (74%) were well appearing. The most common diagnoses were occult bacteraemia [60 (26.9%)] and sepsis [56 (25.1%)]. The most frequent pathogens were *Streptococcus pneumoniae* [68 (30.5%)] and *Neisseria meningitidis* [42 (18.8%)]. Four (1.8) patients died (*S. pneumoniae*, 2) and eight (3.5%) had sequelae (*S. pneumoniae*, 5). The diagnoses and clinical characteristics of the children varied significantly depending on the isolated pathogen. Duration of fever less than 24 h, symptoms other than fever and not being well-appearing upon arrival to the emergency department were independent risk factors for greater severity (area under the receiver operating characteristics curve = 0.805; 95% confidence interval: 0.741–0.868).**

Conclusion **IBIs are commonly diagnosed in previously healthy and well-appearing young children. *S. pneumoniae* was responsible for the majority of deaths or sequelae. Short duration of fever, symptoms other than fever and not being stable on arrival are associated with greater severity. *European Journal of Emergency Medicine* 00:000–000**

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Keywords: invasive bacterial infection, meningitis, occult bacteraemia, sepsis

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Introduction

Fever is a very common reason for consultation among children attending the emergency department (ED) [1]. In most cases, the cause is a self-limiting viral infection. Despite advances in vaccinations and antibiotics, meningitis and sepsis remain significant causes of death of children in developed countries. Early identification of these children is essential to initiate immediate antibiotic therapy. In fact, early recognition and treatment of children with an invasive bacterial infection (IBI) is an imperative for emergency physicians. Nevertheless, identification of patients with an IBI may be difficult. Nowadays, patients with an IBI are often brought to the ED after only a few hours of fever, the signs and symptoms often being difficult to differentiate from benign self-limited febrile illnesses [2]. In addition, most of these patients are younger than 2–3 years of age, at which the manifestations of the different infectious diseases are usually more nonspecific [3].

However, the microorganisms causing the IBIs have changed over the last decades, mostly because of the vaccines developed against the microorganisms responsible for most of them. Thus, the implementation of the *Haemophilus influenzae* b (Hib) conjugate vaccine led to the virtual eradication of this microorganism in vaccinated populations [4]. Subsequent implementation of the routine vaccination policy with pneumococcal conjugate vaccines (PCV, both seven-valent PCV and 13-valent PCV) led to a marked decrease in invasive pneumococcal diseases [5]. Furthermore, meningococcal C conjugate vaccination also significantly decreased the invasive meningococcal infections [6].

Despite the importance of knowing both the clinical and the microbiological characteristics of paediatric patients

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with an IBI, there are no large recent studies published in Europe.

The main objective is to characterize the emergency presentations of IBI among children aged younger than 14 years and their main profiles.

The secondary objective is to identify factors related to a greater severity.

Patients and methods

We carried out a prospective registry-based cohort study that included all the patients aged younger than 14 years diagnosed with an IBI in a paediatric ED between January 2008 and December 2015. Our ED is a tertiary teaching hospital and, each year, receives around 55 000 children younger than 14 years of age.

The results for the first 2 years of this registry were used to describe patients diagnosed with an IBI after the introduction of the PCV7 in Spain [2].

During the period of the study, all patients younger than 14 years of age attending the ED and diagnosed with IBI were identified using the electronic records of our hospital. Each month, a report with all the cultures obtained in the ED was sent by one of the investigators (M.S.) from the Microbiology Service to other ED investigator (S.M.), who identified all the patients with a bacterial pathogen in blood and/or cerebrospinal fluid (CSF) by growth in bacterial culture and/or genomic detection of *Neisseria meningitidis* and *Streptococcus pneumoniae* using the PCR. These episodes were revised by two other investigators (I.G., J.V.) and disagreements were resolved with consensus from a third investigator (S.M.). Information on the patient and the episode was obtained from the electronic clinical records of the paediatric ED and the public health system.

The following data were collected: age, sex, personal history, month and year of consultation, pneumococcal vaccination status, duration of fever, associated symptoms, maximum temperature, previous consultation in the ED, appearance upon arrival, physical exam, microorganism isolated, final diagnosis, destination and evolution of the patient (Supplementary Table 1, Supplemental digital content 1, *http://links.lww.com/EJEM/A157*).

Definitions

(1) IBI: identification of bacterial pathogen in blood and/or CSF by growth in bacterial culture and/or genomic detection of *N. meningitidis* and *S. pneumoniae* using the PCR technique (RealCycler MENE and RealCycler MENELI; Progenie Molecular, Valencia, Spain). Patients with a blood culture in which a bacterial species classically considered a contaminant was isolated (including *Staphylococcus epidermidis*, *Propionibacterium acnes*, *Streptococcus viridans*, *Corynebacterium* spp., and other diphtheroids) were excluded if the samples were collected in otherwise healthy patients. In these immunocompromised children, a definitive diagnosis of catheter-related bloodstream infection required positive percutaneous blood culture results with concordant microbial growth from the catheter tip or catheter-drawn cultures
(2) Previously healthy patient: patients without any of the following risk factors: (a) immunosuppression (oncological illness, chronic renal failure, transplant patient, sickle cell disease); (b) the presence of a mechanical device (indwelling catheter, ventriculoperitoneal shunt, auditory prostheses); and (c) an invasive diagnostic or therapeutic procedure in the previous 10 days.
(3) Well-appearing patients: patients with a stable paediatric assessment triangle upon arrival at the ED [7].
(4) Occult bacteraemia: isolation of pathogenic bacterium in the blood of a well-appearing child with fever without a source (absence of signs of a focal infection).
(5) Sepsis: life-threatening organic dysfunction because of a dysregulated host response to infection [8].
(6) Septic shock: those patients with persisting hypotension requiring vasopressors despite adequate volume resuscitation.
(7) Severity criteria: the following were considered:
    (a) Death.
    (b) Sequelae.
    (c) Admission to the Paediatric ICU (PICU).

The study was approved by the Clinical Research Ethics Committee of the hospital. To maintain patient confidentiality, the database did not include any data that would have allowed the identification of patients. As identities remained anonymous and no intervention was performed on patients, informed consent was not required.

Statistical analysis

The qualitative variables were described using absolute frequencies and percentages and the continuous variables were described using either the mean and SD or median and interquartile range. The χ^2-test was used to study the association between qualitative variables. Poisson regression models were used to analyse incidence rates of pneumococcal IBI for time period.

A multivariate binary logistic regression was performed to identify the independent risk factors related to a greater severity of the process. Death, sequelae and/or admission to the PICU were used as severity criteria. In this way, the outcome measure was the presence of, at least, one of the following: death, sequelae and admission to PICU. A univariate logistic regression analysis was carried out

initially. All variables with P less than 0.2 were subsequently included in a nonautomatic multivariate stepwise model. All variables with P less than 0.05 were included in the final multivariate model. The results of the model are presented as odds ratio and 95% confidence interval (CI). The area under the receiver operating characteristics curve was calculated for the final model. The goodness of fit of the model was evaluated using the Hosmer–Lemeshow test.

All statistical analyses were carried out using the SPSS statistical software package, version 23.0 (IBM, Armonk, New York, USA).

Results

During the study period, 456 830 episodes corresponding to children aged younger than 14 years were registered in the ED. Of these, 223 were diagnosed with an IBI (0.048%, 95% CI: 0.047–0.049) by growth in bacterial culture and/or genomic detection of *N. meningitidis* and *S. pneumoniae* using the PCR. Globally, 187 (83.9%) were previously healthy; there was a slight predominance of males [126 (56.5%)] and the median age was 19 months (interquartile range: 5 months to 2 years). Almost 50% [102 (45.7%)] came to the ED between October and January. The global characteristics of those patients diagnosed with an IBI are shown in Table 1.

S. pneumoniae [68 (30.5%)] and *N. meningitidis* [42 (18.8%), Table 2] accounted for nearly 50% of the IBIs. The rate of pneumococcal IBI changed before and after the implementation of the routine vaccination policy with PCV13 (Fig. 1). A decreasing trend was found for pneumococcal IBI in the period 2008–2015; this was not statistically significant [Incidence rate ratio = 0.911 (95% CI: 0.820–1.013); $P = 0.085$]. *S. pneumoniae* was serotyped in 57 patients, 37 (64.9%) of whom were included in the PCV13.

The final diagnoses, age and clinical characteristics of the patients varied significantly in terms of the isolated bacterial pathogen (Tables 3 and 4).

A total of 147 (65.9%) patients were admitted to hospital (64 in the PICU, 28.7% of all patients).

The vast majority [218 (97.8%)] did well, although four (1.8%) died (28-day mortality) and eight (3.6%) had sequelae (Table 5). Three children with a ventriculoperitoneal shunt experienced a shunt failure, requiring a replacement.

Presenting to the ED during the first 24 h of the disease, the presence of symptoms other than fever and not appearing well upon arrival at the ED were independent risk factors for greater severity (Table 6). This model showed an area under the receiver operating characteristics curve of 0.805 (95% CI: 0.741–0.868) and the P value of the Hosmer–Lemeshow test was 0.356.

Table 1 Characteristics of the patients diagnosed with an invasive bacterial infection

	n (%)	95% CI
Sex (male)	126 (56.5)	50–63
Age: < 12 months	86 (38.6)	32.2–45
Increased risk of invasive bacterial infection		
No	187 (83.8)	78.9–88.6
Immunological and/or with central venous catheter	21 (9.5)	5.6–13.3
Others	15 (6.7)	3.4–9.9
Pneumococcal vaccine dose received		
Unknown	24 (10.8)	6.7–14.8
None	117 (52.5)	45.9–59
1 doses	9 (4)	1.4–6.5
2 doses	13 (5.8)	2.7–8.8
3 doses	29 (13)	8.5–17.4
4 doses	31 (13.9)	9.3–18.4
Duration of fever		
Afebrile	8 (3.6)	1.1–6
< 6 h	64 (28.7)	22.7–34.6
6–24 h	63 (28.3)	22.3–34.2
> 24 h	88 (39.4)	33–45.8
Symptoms		
Fever only	64 (28.7)	22.7–34.6
Respiratory	44 (19.7)	14.5–24.9
Digestive	60 (26.9)	21.1–32.7
Neurological	35 (15.7)	10.9–20.5
Rash	21 (9.4)	5.5–13.2
Osteoarticular and/or soft tissue	19 (8.5)	4.8–12.1
Others	14 (6.3)	3.1–9.5
Well appearing upon arrival at the emergency department	165 (74)	68.2–79.7
Physical examination		
Normal	92 (41.3)	34.8–47.7
Rash	52 (23.3)	17.7–28.8
Abnormal pulmonary auscultation	28 (12.6)	8.2–16.9
Alteration of the central nervous system	32 (14.3)	9.7–18.9
Osteoarticular and/or soft tissue findings	15 (6.7)	3.4–9.9
Others	18 (8.1)	4.5–11.6

CI, confidence interval.

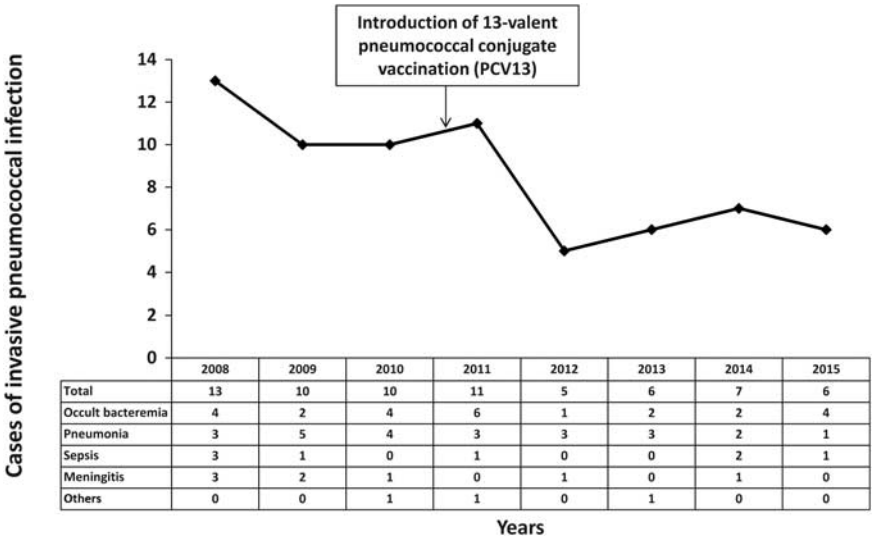
Table 2 Bacteria isolated from patients with an invasive bacterial infection

Bacteria	*n* (%)	95% CI
Streptococcus pneumoniae	68 (30.5)	24.5–36.5
Neisseria meningitidis	42 (18.8)	13.7–23.9
Escherichia coli	33 (14.8)	10.1–19.5
Staphylococcus aureus	25 (11.2)	7.1–15.3
Streptococcus agalactiae	9 (4)	1.4–6.6
Streptococcus pyogenes	9 (4)	1.4–6.6
Staphylococcus coagulase (–)	8 (3.6)	1.1–6.1
Enterococcus faecalis	6 (2.7)	0.6–4.8
Others: 23 (*Salmonella* spp. 5, *Pseudomonas aeruginosa* 3, *Klebsiella* spp. 3, *Proteus mirabillis* 2, *Haemophilus influenzae* 2, *Listeria monocytogenes* 1, *Moraxella catharralis* 1, *Morganella morgagni* 1, *Propionebacterium acnes* 1; *Streptococcus mitis* 1, *Staphylococcus lugdunensis* 1, *Streptococcus salivarius* 1; *Campylobacter jejuni* 1)	23 (10.3)	6.4–14.4

Data are expressed as *n* (%) and 95% CI.
CI, confidence interval.

Meningococcal infections were the most severe IBI (odds ratio: 12.3, 95% CI: 5.3–28.4), as was also the case for patients diagnosed with sepsis or meningitis with respect to other diagnoses (82.1, 44.0 and 7.0%, respectively, $P < 0.001$).

Fig. 1



	2008	2009	2010	2011	2012	2013	2014	2015
Total	13	10	10	11	5	6	7	6
Occult bacteremia	4	2	4	6	1	2	2	4
Pneumonia	3	5	4	3	3	3	2	1
Sepsis	3	1	0	1	0	0	2	1
Meningitis	3	2	1	0	1	0	1	0
Others	0	0	1	1	0	1	0	0

Cases of invasive pneumococcal bacterial infection by year.

Table 3 Isolated bacteria related to the final diagnosis of the patients

	Occult bacteraemia	Sepsis/shock	Pneumonia	Urinary tract infection	Meningitis	Arthritis/ osteomyelitis	Cellulitis/ abscess	Others	Total
Streptococcus pneumoniae	25 (36.8) 25.3–48.26	8 (11.8) 4.1–19.5	24 (35.3) 23.9–46.7	0	8 (11.8) 4.1–19.5	0	0	3 (4.3) 0–9.3	68 (30.5) 24.5–36.5
Neisseria meningitidis	2 (4.8) 0–11.26	30 (71.4) 57.7–85.1	0	0	10 (23.8) 10.9–36.7	0	0	0	42 (18.9) 13.7–23.9
Escherichia coli	2 (6.1) 0–14.2	3 (9.1) 0–18.9	0	26 (78.8) 64.8–92.8	2 (6.1) 0–14.27	0	0	0	33 (14.8) 10.1–19.5
Staphylococcus aureus	8 (32.0) 13.7–50.3	1 (4.0) 0–11.7	1 (4.0) 0–11.7	1 (4.0) 0–11.7	0	13 (52.0) 32.4–71.6	0	1 (4.0) 0–11.7	25 (11.2) 7.1–15.3
Streptococcus agalactiae	2 (22.2) 0–49.4	6 (66.7) 35.9–97.5	0	0	1 (11.1) 0–31.6	0	0	0	9 (4) 1.4–6.6
Streptococcus pyogenes	3 (33.3) 2.5–64.1	2 (22.2) 0–49.4	1 (11.1) 0–31.6	0	0	0	3 (33.3) 2.5–64.1	0	9 (4) 1.4–6.6
Staphylococcus coagulase (–)	5 (62.5) 28.9–96.0	1 (12.5) 0–35.4	0	0	1 (12.5) 0–35.4	0	1 (12.5) 0–35.4	0	8 (3.6) 1.1–6.1
Enterococcus faecalis	4 (66.7) 29–100	0	1 (16.7) 0–46.5	0	1 (16.7) 0–46.5	0	0	0	6 (2.7) 0.6–4.8
Others	9 (39.1) 19.2–59	5 (21.7) 4.8–38.5	0	0	2 (8.7) 0–20.2	0	1 (4.3) 0–12.6	6 (26.1) 8.1–44.1	23 (10.3) 6.3–14.3
Total	60 (26.9) 21.1–32.7	56 (25.1) 19.4–30.8	27 (12.1) 7.8–16.4	27 (12.1) 7.8–16.4	25 (11.2) 7.1–15.3	13 (5.8) 2.7–8.9	5 (2.2) 0.3–4.1	10 (4.5) 1.8–7.2	223

Data are expressed as *n* (%) and 95% CI.
CI, confidence interval.

IBI was diagnosed at a second visit to the ED in 32 (14.3%) patients (13 *S. pneumoniae* and seven *N. meningitidis*). Of these, six were finally diagnosed with sepsis and one died. Four (12.5%) of these 32 patients died or presented sequelae [vs. eight (4.1%) of the 191 diagnosed at the first visit, $P=0.07$].

Discussion

This study shows that IBIs accounts for a very small percentage of children attending a paediatric ED, highlighting the scope of the challenge of identifying rare critical cases in a large population with universal access to a health care system. IBIs are often diagnosed in previously healthy well-appearing young children presenting early to the ED. Most of the children do well. Those children not well appearing, showing symptoms other than fever and attended to in the first 24 h of the fever had a worse outcome. The clinical characteristics, diagnoses and evolution of these patients varied depending on the bacterial pathogen isolated.

The most common isolated pathogen was *S. pneumoniae*, mainly responsible for the cases of occult bacteraemia and invasive pneumonia and, together with *N. meningitidis*, the

Table 4 Clinical characteristics of the invasive infections caused by the most common bacteria

	Streptococcus pneumoniae ($n=68$)[a]	*Neisseria meningitidis* ($n=42$)[b]	*Escherichia coli* ($n=33$)	*Staphylococcus aureus* ($n=25$)[c]	*Streptococcus pyogenes* ($n=9$)	*Streptococcus agalactiae* ($n=9$)
Age (months) [median (interquartile range)] (25–75%)	19 (11.2–35)	20 (7.7–48)	1 (0–9)	84 (18–126)	39 (20–72)	0 (0–1.5)
Previously healthy	66 (97.1)	42 (100)	28 (84.8)	20 (80)	9 (100)	7 (77.8)
Duration of fever < 12 h	21 (30.9)	17 (40.5)	20 (60.6)	7 (28)	3 (33.3)	9 (100)
Fever > 39°C	53 (77.9)	28 (66.7)	12 (36.4)	13 (52)	7 (77.8)	2 (22.2)
Associated symptoms						
None	16 (23.5)	8 (19)	18 (54.5)	7 (28)	0	4 (44.4)
Respiratory	30 (44.1)	4 (9.5)	7 (21.2)	0	0	0
Rash	0	17 (40.5)	0	0	3 (33.3)	0
Neurological	13 (19.1)	13 (31)	1 (3)	1 (4)	1 (11.1)	1 (11.1)
Stable on arrival	42 (61.8)	24 (57.1)	31 (93.9)	24 (96)	7 (77.8)	6 (66.7)
Physical examination						
None	25 (36.8)	8 (19)	27 (81.8)	7 (28)	1 (11.1)	4 (44.4)
Abnormal PA	21 (30.9)	0	0	1 (4)	0	0
Rash	8 (11.8)	32 (76.2)	1 (3)	2 (8)	5 (55.6)	0
CNS alteration	14 (20.6)	2 (4.8)	3 (9.1)	0	0	4 (44.4)
Final diagnosis						
Occult bacteraemia	25 (36.8)	2 (4.8)	2 (6.1)	8 (32)	3 (33.3)	2 (22.2)
Sepsis	8 (11.8)	30 (71.4)	3 (9.1)	1 (4)	2 (22.2)	6 (66.7)
Pneumonia	24 (35.3)	0	0	1 (4)	1 (11.1)	0
Urinary infection	0	0	26 (78.8)	1 (4)	0	0
Meningitis	8 (11.8)	10 (23.8)	2 (6.1)	0	0	1 (11.1)
OAI	0	0	0	13 (52)	3 (33.3)	0
Others	3 (4.4)	0	0	1 (4)	0	0
Evolution						
Death	2 (2.9)	0	0	0	1 (11.1)	0
Sequelae	5 (7.4)	3 (7.1)	0	0	0	0

CNS, central nervous system; OAI, osteoarticular and/or soft tissue infection; PA, pulmonary auscultation.

[a]Occult bacteraemia and meningitis were more common in children aged younger than 2 years (21/25, 84%; and 6/8, 75%, respectively). Most pneumonia cases were found in children aged older than 2 years (16/24; 66%).

[b]The presence of rash varied depending on the final diagnosis for the patient (29 of 30 patients (96.7%) with a final diagnosis of sepsis showed rash compared with 2/10 (20%) with meningitis, $P < 0.0001$).

[c]One of these was methicillin resistant.

main cause of shock and meningitis. The pneumococcal IBIs showed a different pattern depending on the age of the child. Bacteraemia and meningitis were more common in those aged younger than two years and pneumonia among older children. *S. pneumoniae* was involved in more than half the cases of children who died or who suffered sequelae. As a result, preventive actions, especially vaccination, appear essential [9]. A high percentage of the pneumococci isolated corresponded to vaccine serotypes, as noted previously [10]. In addition, the global prevalence of *S. pneumoniae* decreased after the implementation of the PCV13. This decrease would probably have been greater with adequate pneumococcal vaccination coverage of the population [11].

N. meningitidis accounted for the second latest group of IBIs; it was the main cause of sepsis and was associated with greater severity than the other bacteria. In contrast to other studies, which show a higher prevalence of meningococcal infections in children younger than 2 years of age [12], a large number of patients with meningococcal IBI were older than 2 years of age and 25% were older than 4 years. In contrast to other series [13,14], a significant percentage of patients did not develop a rash, mainly in patients diagnosed with meningococcal meningitis, making it more difficult to choose the best option of empirical antibiotics related to the presence or absence of rash [15]. The lower rate of rash in our patients, and perhaps the better overall evolution compared with other studies [16], could at least partially be explained by the fact that our patients are brought to the ED very early.

As it has been reported [17], *Staphylococcus aureus* was associated with osteoarticular and/or soft tissue infections in older children with more prolonged symptoms. Only one of the *S. aureus* isolated in our series was methicillin resistant. Given the recent increase in the prevalence of infections because of methicillin-resistant *S. aureus*, its prevalence must be considered when deciding on the most appropriate antibiotic [18].

As expected [17], infections caused by *Escherichia coli* and *Streptococcus agalactiae* were more common in younger children with fever without a source brought very early to the ED. Most of these patients were previously healthy and did not have a very high temperature.

Not appearing well when evaluated in the ED, the presence of symptoms other than fever and being brought early to the ED were associated with greater severity. This finding highlights the importance of early administration of antibiotics in patients with a suspected IBI.

Table 5 Clinical characteristics of the patients with an invasive bacterial infection who died or developed sequelae

Age (months)	Sex	Previously healthy	Previous visit	Time to progression (h)	Symptoms other than fever	Maximum temperatura (ºC)	Good general condition	Findings in physical examination	Bacteria	Diagnosis	Evolution
3	Male	Yes	Yes	72	Neurological	40.3	No	CNS	*S. pneumoniae*	Sepsis	Death
15	Female	Yes	No	8	Gastrointestinal	40	No	Signs of shock and rash	*S. pyogenes*	Sepsis	Death
114	Male	No	No	< 1 h	Headache	40.3	Yes	None	*S. pneumoniae*	Sepsis	Death
156	Female	No	No	Afebrile	Gastrointestinal	37.5	No	None	*M. morgagni*	Sepsis	Death
4	Female	Yes	No	24	Neurological	39	No	Signs of shock	*S. pneumoniae*	Meningitis	Hydrocephalus, deafness, endocarditis, VP shunt
8	Female	Yes	No	24	Rash	38.2	No	CNS and rash	*N. meningitidis*	Sepsis	Terminal kidney failure, transplant
24	Male	Yes	No	120	Respiratory	39.5	No	CNS and auscultation	*S. pneumoniae*	Sepsis	Necrotizing pneumonia, bronchopleural fistula
24	Male	Yes	Yes	120	Respiratory and digestive	40.2	No	CNS	*S. pneumoniae*	Pneumonia	Necrotizing pneumonia, bronchopleural fistula
37	Male	Yes	No	240	Respiratory and digestive	40	Yes	CPA	*S. pneumoniae*	Endocarditis	Valve replacement, metal prosthesis
39	Male	Yes	Yes	144	Respiratory	39	No	CPA and CNS	*S. pneumoniae*	Sepsis	Necrotizing pneumonia, bronchopleural fistula
64	Female	Yes	No	20	Gastrointestinal	39.2	No	CNS	*N. meningitidis*	Meningitis	Deafness
73	Female	Yes	Yes	16	Rash	39	No	Signs of shock and rash	*N. meningitidis*	Sepsis	Tissue necrosis

CNS, central nervous system; CPA, cardiopulmonary auscultation; CR, cardio-respiratory; VP shunt, ventriculoperitoneal shunt.

A worrisome finding was the number of children with a previous ED visit before diagnosis. Although this percentage was lower than reported previously [19], the patients diagnosed at a second visit in our study had a higher mortality and sequelae rate, although the differences were not significant. It has been suggested that progression to sepsis or meningitis in well-appearing children is unpredictable and therefore a careful clinical evaluation should normally be sufficient and the most appropriate at the first visit of a child with fever [20]. However, in light of our findings, it is advisable to recommend close monitoring by the parents in the following hours after the ED evaluation of febrile children and subsequent assessment by a primary care physician.

Our series has some limitations. First, it is a single-centre study with the limitations inherent to such studies. Thus, the rate of IBI is low, but we have to consider that the access to the ED in our country is free (it is not necessary to be sent from primary care or prehospital emergency settings) and around 20% of children admitted to our ED are trauma patients. Despite this, we consider that the findings are likely to be similar in other hospitals in Europe with similar vaccine coverage. Second, given the low incidence of occult bacteraemia in infants aged 3–24 months with fever without a source, in 2014, we increased the temperature cut-off point for collecting a blood culture, thus resulting in a marked reduction in the number thereof. However, the decrease in pneumococcal IBIs was not exclusively because of the decrease in the number of patients with occult bacteraemia as a decrease in other pneumococcal IBIs was also found, thus suggesting that the effect of the PVC13 is in agreement with published findings. Similarly, the low prevalence of opportunistic microorganisms in our series is mainly because of the fact that oncological patients were mainly managed by the paediatric oncology unit. However, we did not analyse the patients with a suspected invasive bacterial infection with no bacteria identified in blood or CSF. This would have enabled us to identify factors associated with a greater probability of having or not having an IBI, but this was not the objective of this study. We did not include some children who did not grow any organisms, but would have been defined as having sepsis (i.e. some extremely unwell children presenting who may have received antibiotics before cultures were obtained). This may impact on the overall burden of disease. Finally, as this is a retrospective study, data collection could occasionally have been improved. However, the fact that it is based on a prospective registry, the availability of electronic clinical records of the pediatric ED and the public health system electronic database enabled exhaustive data collection. This prospective registry has facilitated to get over the limitations due to the sample size found for the study conducted during the first 2 years [2].

Table 6 Univariate and multivariate analyses to identify the risk factors for severity in children diagnosed with an invasive bacterial infection

	Univariate		Multivariate	
	P	OR (95% CI)	*P*	OR (95% CI)
Age (>24 months)	0.691	1.123 (0.633–1.994)		
Sex (female)	0.257	1.395 (0.785–2.481)		
Previous visit to the emergency department	0.162	1.736 (0.802–3.759)		
Duration of fever (< 24 h)	0.080	1.740 (0.937–3.233)	< 0.001	4.082 (1.859–8.964)
Symptoms other than fever	< 0.001	4.935 (2.114–11.523)	0.005	3.869 (1.507–9.938)
Physical examination (altered)	< 0.001	4.825 (2.398–9.705)		
Temperature recorded upon arrival at the emergency department (≥39)	0.025	2.199 (1.104–4.382)		
Maximum temperature at home (< 39)	0.552	1.206 (0.651–2.234)		
Well-appearing (no)	< 0.001	8.910 (4.543–17.478)	< 0.001	8.286 (3.737–18.370)
Patient previously healthy (no)	0.062	2.421 (0.957–6.125)		

CI, confidence interval; OR, odds ratio.

In conclusion, paediatric IBIs currently present more frequently in previously healthy young children, with a clinical and epidemiological pattern that is highly dependent on the age of the patient and the bacterium isolated. The evolution of children with an invasive infection was generally good, although those patients who consulted with a shorter time to progression, symptoms other than fever or who did not present a good general condition upon arrival at the ED were associated with more severe processes. *Pneumococcus* spp. was responsible for more than half of the cases that resulted in death or the appearance of sequelae in these children.

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Conflicts of interest

There are no conflicts of interest.

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despite the highly variable baseline microbiota of patients with a tracheostomy.[7]

The traditional reductionist approach of categorizing ARIs as either viral or bacterial may be too simplistic a clinical framework for ARIs in individuals with a tracheostomy, and possibly all people with ARIs.[7] On D1 of ARI, the majority of the current prospective cohort had a virus detected and a "bloom" of already present genera (ie, *Haemophilus* and *Moraxella*). The tracheal finding of *Haemophilus* and *Moraxella* blooming are consistent with findings from previous studies utilizing nasopharyngeal samples to examine acute respiratory illness outcomes.[9] And although viral–bacterial interactions during ARIs have been described,[10] the present results extend previous research by suggesting that these ARIs were not infections due to acquisition of a new bacterial pathogen as Koch's postulates suggest, but rather a bloom of colonizing genera in the context of a viral infection. Conceptualizing ARIs as "blooms" may be more complex to operationalize clinically than the current reductionist approach, but may eventually provide opportunities for novel, targeted treatment methods. Although beyond the scope of these data, ARIs may be best understood as an emergent phenomenon[7] that (1) is driven by a complex interplay among the infecting virus, microbiome and host response[9] and (2) results in a continuum of ARI severity anchored by pneumonia.

The next step is to better understand the pathobiology of ARI in this high-risk population with variable underlying microbiota to develop novel targets for ARI treatment and to provide guidance about when to use antimicrobials and which bacteria to treat. Until this time of improved ARI understanding and clinical guidance, many clinicians will continue to overuse and misuse antimicrobials for ARIs in children with a tracheostomy.

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PREVALENCE OF OCCULT BACTEREMIA IN INFANTS WITH VERY HIGH FEVER WITHOUT A SOURCE

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Abstract: We carried out a prospective registry-based cohort study at the emergency department of 363 previously healthy well-appearing infants 3–24 months of age with fever without a source ≥40.5°C based on local protocol. Four were diagnosed with occult bacteremia (1.1%; 95% confidence interval: 0–2.2). Recommendations for nontesting for occult bacteremia screening in these children may have to be reconsidered when fever ≥40.5°C. Larger studies are needed to confirm these results.

Key Words: occult bacteremia, very high fever, fever without source, infants

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After the introduction of the pneumococcal conjugate vaccines (PCVs), pneumococcal invasive infections in febrile infants, including occult bacteremia (OB), declined dramatically.[1–3] In a cost-effectiveness study, it was stated that when the rate of OB in febrile infants falls below 0.5% strategies that use empiric testing and treatment should be eliminated.[4] On the other hand, if bacteremia rate is over 1.5%, it is cost-effective to obtain blood tests.[4] Currently, in vaccinated populations, the rate of OB in febrile infants is less than 0.5%. Nevertheless, these studies included infants with temperature greater than 39°C, and it is known that the prevalence of bacteremia increases at higher temperatures.[5] To our knowledge, no study has addressed the rate of OB in well-appearing, highly febrile infants in the era of PCV. The objective of this study is to analyze the prevalence of OB in previously healthy well-appearing infants 3–24 months of age with fever without a source (FWS) equal or higher than 40.5°C in the era of PCV.

PATIENTS AND METHODS

We carried out a registry-based cohort study at the pediatric emergency department (ED) of a tertiary level teaching hospital attending 55,000 visits annually. We included all previously healthy well-appearing infants 3–24 months of age with FWS ≥40.5°C brought to the ED between 2013 and 2016.

Each month, all the febrile infants with a blood culture obtained were identified using the electronic databases of the Microbiology Service and the ED. After that, the main investigator selected for inclusion all infants 3–24 months of age with FWS ≥40.5°C with a blood culture obtained when evaluated in the ED.

To check that all infants 3–24 months of age with FWS ≥40.5°C were included, we also reviewed a randomized sample of the patients coming to the ED during the period of the study. In this way, we revised all the episodes of children admitted to the ED 1 week per month during the period of the study.

We collected the following data from the electronic clinical records of our ED: age, gender, personal history, PCV status, duration of fever, associated symptoms, temperature, previous consultation in the ED, appearance on arrival, physical examination, different blood tests (white blood cell count, absolute neutrophil

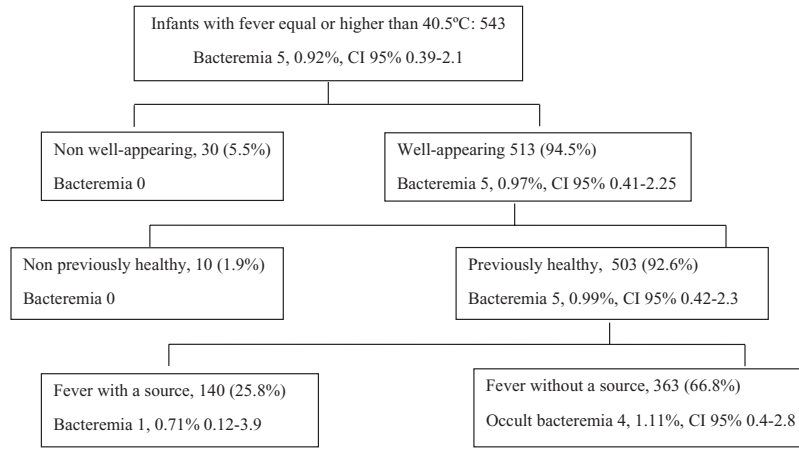

FIGURE 1. Patients' flow chart.

cell count, C-reactive protein and procalcitonin), microorganism isolated, final diagnosis and disposition of the patient.

In our ED, we recommend blood culture, white blood cell, absolute neutrophil cell, serum C-reactive protein, procalcitonin, urine dipstick and polymerase chain reaction for pneumococcus and meningococcus in all febrile infants 3–24 months old with FWS ≥40.5°C, regardless their vaccination status. Other tests (urine culture, chest radiograph, cerebrospinal fluid examination) were obtained at the discretion of the physician in charge.

Definitions

- Previously healthy patients: patients without any of the following risk factors: immunosuppression (oncologic illness, chronic renal failure, transplant patient, sickle cell disease), the presence of a mechanical device (indwelling catheter, ventricle-peritoneal shunt, auditory prostheses) and an invasive diagnostic or therapeutic procedure in the previous 10 days.
- Well-appearing patients: patients with a stable pediatric assessment triangle upon arrival at the ED. Pediatric assessment triangle is a rapid tool recommended by the American Academy of Pediatrics to assess the first general impression of any child. The appearance, the work of breathing and the circulation to the skin are evaluated using specific predefined physical, visual or auditory findings. If any of these 3 components is abnormal, the patient is considered unstable.
- FWS: axillary or rectal temperature higher than 38°C registered at home or in the ED, without associated respiratory symptoms, diarrhea process and findings on physical examination that allows identifying the source of the fever.
- OB: isolation of pathogenic bacterium in the blood of a well-appearing child with FWS.

PCV13 was included in the public immunization program in January 2013. Currently, PCV vaccination coverage in the Basque Country is around 95%.

We carried out the statistical analysis using the statistical program SPSS 23, Chicago, IL. The qualitative variables were described using absolute frequencies and percentages and the continuous variables were described using both the mean and standard deviation or median and interquartile range. The χ^2 test was used to study the association between qualitative variables.

The Clinical Research Ethics Committee of the hospital approved the study. To maintain patient confidentiality, the database did not include any data that would have allowed the identification of patients. As identities remained anonymous and no intervention was performed on patients, informed consent was not required.

RESULTS

During the study period, blood cultures were obtained on 543 infants 3–24 months of age with fever ≥40.5°C, including all the 363 previously healthy well-appearing infants with FWS ≥40.5°C (Fig. 1).

Mean age of the 363 previously healthy well-appearing infants with FWS ≥40.5°C was 13.9±4.9 months and 189 (52.1%) were female. PCV dosing was unknown in 23 (6.3%), and 51 (14%) had not received any dose. Fever duration was shorter or equal than 48 hours in 297 (81.8%). Most common final diagnoses were FWS 282 (77.7%); urinary tract infection 36 (9.9%); fever and rash 16 (4.4%); pneumonia 13 (3.6%) and bacteremia 4 (1.1%). All patients did well.

Four previously healthy well-appearing infants with FWS ≥40.5°C were diagnosed with OB (OB prevalence: 1.1%; 95% confidence interval [CI]: 0–2.2): 3 pneumococcal OB (one 16-month-old non-PCV vaccinated girl, and two 16-month and 19-month-old fully vaccinated girls; pneumococcal OB prevalence: 0.82%; 95% CI: 0%–1.8%) and a 12-month-old boy with a nontype b *Haemophilus influenza* bacteremia. All were managed as outpatients (3 of them after receiving 1 dose of IM ceftriaxone as a result of alterations of the blood biomarkers) and all did well.

Among those 289 infants who have received at least 1 dose of PCV, 2 were diagnosed with pneumococcal OB (0.69%; 95% CI: 0–1.6).

During the study period, blood cultures were also obtained in 140 previously healthy well-appearing infants with fever with a source ≥40.5°C (mainly respiratory symptoms). Blood culture was positive for *Streptococcus pneumoniae* in one 19-month-old boy fully vaccinated infant diagnosed with mastoiditis.

DISCUSSION

Although being lower than the reported in the pre-PCV studies,[4] the rate of OB in previously healthy well-appearing infants 3–24 months of age with FWS equal or higher than 40.5°C does not support the recommendation for not testing these infants to identify those at higher risk for OB. Even though the rate of bacteremia in fully PCV-immunized infants is 0.5% or greater.

Nowadays, most guidelines recommend not testing fully immunized (including PCV) febrile infants and do not give any specific recommendation for those with very high fever.[6] In fact, laboratory evaluation and empiric antibiotic therapy do not significantly

alter the likelihood of progression to focal bacterial infection and are no longer recommended in an otherwise healthy child with FWS who is completely immunized.[7] In addition, since the routine immunization of children with PCV7 or PCV13 vaccine, pathogens other than *S. pneumoniae* have being reported to be the cause of the majority of cases of unsuspected bacteremia.[8] In our study, 4 previously healthy well-appearing infants 3–24 months of age with FWS equal or higher than 40.5°C were diagnosed with OB, 3 of them caused by *Streptococcus pneumoniae*. Two were fully immunized. These results emphasize the importance to rule out serious bacterial infection in young high feverish children, including OB, and highlight the relevance of pneumococcal infection in this selected population in the era of the PCV.

Our study shows certain limitations. The main limitation is the sample size. The CIs of the obtained bacteremia rate do not allow giving a strong recommendation for this population. Nevertheless, the results obtained emphasize the importance to carry out a larger study, preferably multicenter, to establish if nontesting strategy is adequate when fever is over 40.5°C. On the other hand, this is a unicenter study. Nevertheless, results should be similar in populations with similar vaccination status. Finally, to include all the patients in a prospective way, collecting the data when the infants are in the ED would have been more adequate to include all patients. Nevertheless, with the random revision of the episodes registered in the ED, we think that only very few patients were missed, if any.

We conclude that, despite recommendations for nontesting for pneumococcal OB screening in well-appearing febrile infants, these recommendations may have to be reconsidered in infants with FWS ≥40.5°C, including those fully vaccinated. Larger and preferably multicenter studies are needed to confirm these results. Accordingly, a prospective multicenter study will begin on 2018 under the scope of the Research network of the Spanish Society of Pediatric Emergency Medicine (Red de Investigación de la Sociedad Española de Urgencias de Pediatría-Spanish Pediatric Emergency Research Group RISEUP-SPERG).

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I.K. conceptualized and designed the study, supervised data collection, analyzed the data, wrote the initial draft of the manuscript and approved the final manuscript as submitted. E.R. collaborated in the design of the study, collected data, critically revised the manuscript and approved the final manuscript as submitted. A.Z. collected data, critically revised the manuscript and approved the final manuscript as submitted. J.B. collaborated in the design of the study, critically revised the final manuscript and approved the final manuscript as submitted. S.M. conceptualized and designed the study, analyzed the data, revised multiple versions of the initial manuscript and approved the final manuscript as submitted.

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CARDIAC AND PULMONARY CYSTIC ECHINOCOCCOSIS WITH MASSIVE OBSTRUCTION OF THE PULMONARY VESSEL SYSTEM IN A 16-YEAR-OLD GIRL

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Abstract: We describe herein the management of a 16-year-old girl with cystic echinococcosis of the right ventricle and massive obstruction of the pulmonary vessel system by parasitic metastatic dissemination. After resection of the cardiac cyst, pulmonary thromboendarterectomy was performed to remove parts of the obstructive parasitic material. The treatment reduced the elevated pulmonary arterial pressure, improving the patient's overall condition.

Key Words: cystic echinococcosis, thromboendarteriectomy, pulmonary intravascular cyst, cardiac cyst, albendazole, praziquantel

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Cystic echinococcosis (CE), caused by *Echinococcus granulosus*, is a common parasitic disease with high incidence rates in rural areas in Southern Europe, Middle East, Asia and Africa.[1,2] In rare cases, it primarily affects the heart. Ruptures of the cyst membranes can lead to cardiac tamponade, anaphylactic shock or embolization and obstruction of pulmonary vessels, resulting in severe cardiopulmonary symptoms.[3,4] Here, we present a complex case with cardiac and pulmonary involvement and massive obstruction of the pulmonary arteries.

CASE REPORT

A 16-year-old previously healthy female was admitted to our hospital with a 2-month history of increasing dyspnea and coughing. She grew up in a CE endemic area in Romania and moved to Austria 2 years ago. She lived together with her family and was working as a waitress.

Physical examination showed normal weight and height, normal heart rate, no cardiac murmur, normal blood pressure, normal breathing, no dyspnea at rest and no edema. Oxygen saturation was 93%–96% at normal respiratory rate.

Chest radiograph showed multiple intrapulmonary nodules in both lungs and widening of the upper mediastinum. Echocardiography revealed a cystic lesion in the apex of the right ventricle (Fig. 1A). Thoracic computed tomographic scan displayed a cystic

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COVID-19 infection in children shows unique features. All published series agree on its usual mildness, with a high proportion of asymptomatic patients and very low mortality. However, an association between SARS-CoV-2 infection and the appearance of a very serious clinical picture, called pediatric multisystem inflammatory syndrome, has been described.[2,7] Pathophysiology of MIS-C is still unclear. In a recent case series, children with MIS-C had significantly higher SARS-CoV-2 binding and neutralizing antibodies than children with COVID-19 or Kawasaki Disease. MIS-C might be different from other syndromes with similar clinical appearances, with features including an age at onset greater than 7 years, diffuse cardiovascular involvement and elevated quantitative SARS-CoV-2 binding and neutralizing antibodies.[8]

Gastrointestinal symptoms are increasingly recognized to be associated with the presentation of MIS-C. In 2 recently reported series of 35 and 44 pediatric patients with MIS-C, more than 80% showed some type of digestive involvement.[9,10] In our study, 11 patients with MIS-C were included, all of them showing GI symptoms.

Our study has several strengths. It is a multicenter study, involving 15 hospitals in Spain, one of the most impacted countries during the pandemic in Europe. As a consequence, our sample is probably the largest published in pediatric hospitalized patients with COVID-19.

As a limitation of the study, we want to acknowledge the fact that although the development of the project started early in the course of the pandemic in Spain, the majority of the data were retrospectively retrieved.

In conclusion, gastrointestinal symptoms are frequent in COVID-19 pediatric patients admitted to hospital. These symptoms are also predictive of severity, regardless to other confounding factors.

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OCCULT BACTEREMIA IN YOUNG CHILDREN WITH VERY HIGH FEVER WITHOUT A SOURCE: A MULTICENTER STUDY

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Abstract: We carried out a prospective multicenter study including 203 previously healthy well-appearing children who were 3–24 months old with fever without a source ≥40.5°C. Thirty-one (15.3%, 95% confidence interval 11.0–20.9) were diagnosed with serious bacterial infection, including 6 with bacteremia (3%, 95% confidence interval 1.4–6.3). Testing for occult bacteremia in children 3–24 months old with fever without a source should be considered when fever at ≥40.5°C.

Key Words: prevalence, occult bacteremia, very high fever, pneumococcal

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The rate of occult bacteremia in young febrile children has declined dramatically after the introduction of the pneumococcal conjugate vaccines (PCV).[1–3] In this way, strategies that use empiric testing and treatment in young febrile children with temperature higher than 39°C are no longer recommended.[4,5] Nevertheless, previous to the PCV era, the prevalence of bacteremia increased at higher temperatures.[6] Currently, in a unicenter study, the rate of occult bacteremia in previously healthy well-appearing young children who were 3–24 months old with fever without a source (FWS) ≥40.5°C was 1.1% [95% confidence interval (CI) 0–2.2],[7] being PCV vaccination coverage in Spain around 98%.[8] Though, before re-considering the recommendation for testing these young children for occult bacteremia, a multicenter was warranted.

The main objective was to analyze the prevalence of occult bacteremia in previously healthy well-appearing young children 3–24 months of age with FWS equal or higher than 40.5°C in the era of PCV.

PATIENTS AND METHODS

We carried out a multicenter, prospective, observational study at 6 Spanish pediatric emergency departments (ED) on behalf of the Infectious Diseases Working Group of the Spanish Society

TABLE 1. Characteristics of Patients Diagnosed With Bacteremia

Age (Months)	Sex	Duration of Fever (Hours)	PCV Status	Meningococcal Vaccine	Urine Dipstick	WBC	ANC	CRP	PCT	Antibiotic Received	Admission to Ward	Bacteria	Disposition
13	Female	18	3 doses	1 dose	Normal	18,400	9300	75.9	0.23	Yes. Ceftriaxone	No, outpatient	*Streptococcus pneumoniae* (serotype unknown)	Discharge, no sequelae
14	Male	48	3 doses	2 doses	Normal	16,800	12,000	259.1	9.52	Yes. Ceftriaxone	Yes	*Streptococcus pyogenes*	Discharge, no sequelae
11	Female	24	3 doses	1 dose	Normal	24,600	13,100	31.8	3.10	Yes. Ceftriaxone	No, outpatient	*Streptococcus pneumoniae* (serotype 24F)	Discharge, no sequelae
13	Female	18	2 doses	2 doses	Non performed	9400	6100	320	32	Yes. Ceftriaxone	Yes	*Neisseria meningitidis* (serogroup unknown)	Discharge, no sequelae
16	Male	20	3 doses	No	Normal	25,700	22,200	66	5.96	Yes. Ceftriaxone	Yes	*Streptococcus pneumoniae* (serotype 38)	Discharge, no sequelae
23	Female	48	3 doses	No	Normal	18,500	11,100	77.5	0.19	Yes. Ceftriaxone	No, outpatient	*Moraxella spp.*	Discharge, no sequelae

of Pediatric Emergencies, endorsed by the Research network of the Spanish Society of Pediatric Emergency Medicine.

Patients were prospectively enrolled starting from January 1, 2018 to December 31, 2019. We included all previously healthy well-appearing 3–24-month-old children with FWS ≥40.5°C brought to the ED.

We collected the following data from the patient ED episode: age, sex, personal history, vaccination status, duration of fever, associated symptoms, temperature, previous consultation in the ED, appearance on arrival, physical examination, supplementary tests, isolated microorganism, final diagnosis and disposition of the patient. We monitored the progress of the patients by reviewing the medical records of those who were admitted to ward, and by primary care medical reports and conducting telephone interviews for those who were managed as outpatients. Interviews were performed within a month after the visit to the ED.

Obtaining a blood culture in the included children was mandatory and we also recommended to obtain the following tests: white blood cell count (WBC), absolute neutrophil count (ANC), serum C-reactive protein (CRP) and procalcitonin (PCT). These tests were considered to be altered if WBC was lower than 5000/µL or higher than 15,000/µL, ANC >10,000/µL, CRP >20 mg/L and PCT >0.5 ng/mL. The polymerase chain reaction for pneumococcus and meningococcus was obtained in those EDs in which this test was available. Urine dipstick was performed in all 3–24-month-old female and 3–12-month-old male children. Other tests (urine culture, chest radiograph, cerebrospinal fluid examination) were obtained at the discretion of the physician in charge.

All included children had specific electronic questionnaires completed via Google Drive by the physicians in charge of their care. Questionnaires were initially distributed to all participating EDs seeking to ensure the clarity of the methods and to enhance the quality of the data collected. The questionnaires were then completed by the physician after ED discharge for patients discharged home, and after hospital discharge for patients admitted to the hospital, to obtain complete information on patient characteristics and ED and outcomes. The completed questionnaires were then sent to the principle investigator (I.G.).

Definitions were explained in the previous manuscript.[7] FWS was considered in febrile children without associated respiratory symptoms (including rhinorrhea or nasal congestion), diarrhea process and findings on physical examination (including acute otitis media) that allows identifying the source of the fever. We considered to be previously healthy patients those without any of the following risk factors: immunosuppression (oncologic illness, chronic renal failure, transplant patient, sickle cell disease), the presence of a mechanical device (indwelling catheter, ventricle-peritoneal shunt, auditory prostheses) and an invasive diagnostic or therapeutic procedure in the previous 10 days. For this study, we considered serious bacterial infection those children finally diagnosed with bacteremia, urinary tract infection, bacterial meningitis or pneumonia.

We carried out the statistical analysis using the statistical program SPSS 23, Chicago, IL. We described the categorical variables using absolute frequencies and percentages and the continuous variables using both the mean and standard deviation or median and interquartile range. We used the χ^2 test to study the association between categorical variables.

The Clinical Research Ethics Committee of the Basque Country approved the study (internal code PI2017169). Approval for study and data sharing with the coordinating institution and with the centralized data center was granted by the institutional review board at each participating institution. To maintain patient confidentiality, the forms did not include any data that would have allowed the identification of any patient.

RESULTS

During the study period, we registered 344,500 episodes in the 6 pediatric EDs. Of them, 203 corresponded to children 3–24 months of age with FWS equal or higher than 40.5°C. Mean age was 14 ± 4.6 months old and 110 (54.2%) were male. Two hundred (98.5%) had received at least 1 PCV dose and 103 (50.7%) had a duration of the fever less than 24 hours. Thirty-one (15.3%, 95% CI 11.0–20.9) were diagnosed with serious bacterial infection: urinary tract infection 14 (6.9%), pneumonia 11 (5.4%) and bacteremia 6 (3%). All blood tests (CRP, PCT, WBC and ANC) were obtained in 192 children. Thirty (15.6%) did not show any alteration of the tests, including 1 child diagnosed with pneumonia and 1 with UTI. Lumbar puncture was performed in 3 patients (negative cultures); urine dipstick in 169 (83.3%), urine culture in 75 (36.9%) and chest radiography in 97 (47.7%).

The characteristics of young children diagnosed with bacteremia are shown in Table 1. All children with bacteremia had, at least, 1 blood test altered (sensitivity 100%, 95% CI 51.7–100; specificity: 16.1%, 95% CI 11.3–22.4; PPV: 3.7%, 95% CI 1.5–8.2). All febrile children with bacteremia did well. Of the 6 children diagnosed with occult bacteremia, 3 corresponded to children with pneumococcal occult bacteremia [prevalence 1.48%; (95% CI 0.5–4.3)].

DISCUSSION

The rate of occult bacteremia in previously healthy well-appearing children 3–24 months of age with FWS equal or higher than 40.5°C supports the recommendation for testing these children for occult bacteremia, regardless the PCV vaccination status. The results of our study confirm those obtained in the previous unicenter study.[7] In addition, all the children diagnosed with occult bacteremia were fully PCV vaccinated, including those with pneumococcal occult bacteremia. Pneumococcal occult bacteremia may occur in PCV fully vaccinated children.[9] In fact, PCV13 serotypes continue to account for nearly a quarter of invasive pneumococcal infection in US children 4–7 years after PCV13 was introduced, mainly otherwise healthy children despite receiving ≥2 PCV13 doses.[9]

Recommendation for no additional testing beyond evaluation of the urine should be reconsidered in children 3–24 months with FWS ≥40.5°C. The role of blood tests to guide initial clinical decision-making in these patients, like administering antibiotics, should be determined. In the pre-PCV era, one option for the management for young febrile children higher than 39°C was to administer antibiotics to those young children with altered WBC and/or ANC[10], although positive predictive value of test results was poor. Currently, new tests are often used to evaluate febrile children at risk for invasive bacterial infection at the ED. It would be interesting to know if PCT and CRP are more adequate to identify young children with high fever at high risk for bacteremia. In our study, all the children with occult bacteremia showed alterations of the biomarkers, but global performance of the tests was also poor.

Our study shows certain limitations. The main limitation of our study is the sample size. In the previous unicenter study,[7] we commented that larger and multicenter studies were necessary to confirm the results obtained. In this way, when designing this prospective multicenter study our intention was to include around 1000 patients. After including 200 patients with a rate of bacteremia around 3%, we thought that it was not adequate to continue recruiting patients and not publishing our results.

We conclude that previously healthy and well-appearing 3–24-month-old children with FWS equal or higher than 40.5°C should be tested for occult bacteremia regardless of their PCV vaccination status.

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PLASMAPHERESIS FOR RESCUE IN SEVERE ENCEPHALOPATHY AND MULTIORGAN FAILURE FROM FULMINANT INFLUENZA (H3N2) INFECTION

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Abstract: We are presenting a case of 4-years-old previously healthy male with coma, severe acute hepatitis and multiorgan failure in presence of Influenza infection. Literature review highlighted an immune-mediated pathophysiology for such presentations so the child underwent a trial of plasmapheresis which resulted in a rapid clinical improvement and child was discharge in his baseline neurologic status by day 14.

Key Words: immune mediated encephalitis, plasmapheresis, influenza, multiorgan dysfunction

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REGULAR ARTICLE

ACTA PÆDIATRICA NURTURING THE CHILD WILEY

Paediatric *Escherichia coli* bacteraemia presentations and high-risk factors in the emergency department

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Abstract

Aim: *Escherichia coli* (*E coli*) is a known cause of paediatric bacteraemia. The main objective was to characterise the emergency department (ED) presentations of paediatric *E coli* bacteraemia and secondarily to identify those related to greater severity.

Methods: This was a sub-study of a multicentre cross-sectional prospective registry including all with *E coli* bacteraemia episodes between 2011 and 2016. We used multiple correspondence and cluster analysis to identify different patterns.

Results: We included 291 patients and 43 met criteria for severe disease (14.3%, 95% confidence interval 11.2-19.3). We identified four types of paediatric *E coli* bacteraemia presentations. Two (178 patients, 61.2%) were related to well-appearing previously healthy infants with associated urinary tract infection (UTI). Well-appearing children older than 12 months old with underlying disease (n = 60, 20.6%) and non-well-appearing children of different ages (n = 53, 18.2%) corresponded to the other two types; these had associated UTI infrequently and higher severity rate (15% and 50.9%, respectively, higher when compared with the two previous types, $P < .01$), including the two patients who died.

Conclusion: There were four different types of ED paediatric *E coli* bacteraemia presentations with different severity. Febrile young children with associated UTI showed the best outcome.

KEYWORDS

bacteraemia, *Escherichia coli*, outcome, risk factor, urinary tract infection

1 | BACKGROUND

Fever is a very common reason for consultation among children attending the emergency department (ED). In most cases, the cause is a self-limiting viral infection. Despite advances in vaccinations and antibiotics, invasive bacterial infections remain significant causes of death of children in developed countries. General infant immunization programmes against the most common pathogens (*Haemophilus influenzae type b*, *Streptococcus pneumoniae* and *Neisseria meningitides*) have led to a significant decrease of childhood invasive

Abbreviations: *E. coli*, Escherichia coli; ED, emergency department; ICU, intensive care unit; UTI, urinary tract infection.

bacterial infections[1,2] and changes in the distribution of most frequently isolated pathogens.

Escherichia coli is a known cause of bacteraemia in febrile infants under 12 months of age[3] and has been widely reported mainly in febrile infants <3 months of age, many of them associated with a urinary tract infection (UTI).[4,5] In a previous study under the scope of the Spanish Society of Emergency Medicine, *E coli* accounted for 20% of the bacteraemia episodes registered in previously healthy children in Spanish EDs.[6] To our knowledge, no large series have analysed the clinical presentation and outcome of children with *E coli* bacteraemia. Our study may help to better identify these children in the ED, especially those at higher risk for severe disease.

The main objective was to characterise the ED presentations of paediatric *E coli* bacteraemia. The secondary objective was to identify presentations related to higher severity.

Our hypothesis was that there are different profiles of paediatric *E coli* bacteraemia presentations with different risk for severe illness.

Key notes

- We characterised the emergency department presentations of paediatric *E coli* bacteraemia and identified those related to greater severity in 291 patients <18 years of age.
- We identified four types of presentations related to previous illnesses, age, sex, appearance upon the arrival and association with urinary tract infection.
- Association with urinary tract infection in febrile well-appearing previously healthy young children showed the best outcome.

2 | PATIENTS AND METHODS

We performed a secondary analysis of a large, multicentre, cross-sectional prospective registry of childhood bacteraemia presentations to 23 Spanish EDs.

In 2010, the Spanish Society of Paediatric Emergency Medicine proposed the establishment of a prospective multicentre registry of positive blood culture obtained at Spanish paediatric EDs. Patients between 0 months and 20 years were prospectively enrolled between 2011 and 2016. During 2011, 15 paediatric EDs participated in the recruitment, 22 during 2012, 21 during 2013, 19 during 2014, 17 during 2015 and 13 during 2016.

Blood culture technique was explained in the study published in 2014.[6]

For the purpose of this study, we included those children with *E coli* isolated in the blood culture.

We used the Paediatric Assessment Triangle (PAT) to assess the first general impression of the child. The PAT is a rapid tool recommended by the American Academy of Pediatrics to assess the first general impression of any child. The appearance, the work of breathing and the circulation to the skin are evaluated using specific predefined physical, visual or auditory findings. If any of these three components are abnormal, the patient is considered as non-well appearing.[7]

Certain factors were considered as increasing the risk of having a bacteraemia. These factors included immunosuppression such as oncological illness, chronic renal failure, transplant patient and sickle cell disease; the presence of a mechanical device, such as an indwelling catheter or a ventriculo-peritoneal shunt; an invasive diagnostic or therapeutic procedure in the previous 10 days; a serious kidney or urinary tract malformations such as double renal system, severe bilateral vesicoureteral reflux and presence of ureterostomy or vesicostomy; and patients with multiorgan syndromes or systemic illness. For the purpose of this study, patients without any of these risk factors were considered previously healthy.

We defined occult bacteraemia as isolation of *E coli* in the blood in the absence of an identifiable focus of infection. A new positive blood culture after adequate antibiotic treatment (sensitive antibiogram and adequate dose and duration of the antibiotic) was considered as a new episode of bacteraemia.

For the purpose of this study, we adapted the sepsis criteria published by Goldstein et al[8] A patient with a positive blood culture was diagnosed with sepsis if presenting with any of the following signs: tachycardia >180 bpm not due to external or painful stimuli or long-term medication; bradycardia <100 bpm not due to external vagal stimulus, β-blocker drugs or congenital heart disease (only applicable in infants younger than 1 year old); tachypnoea >50 rpm; and signs of organ dysfunction as listed in the aforementioned publication.[8]

Septic shock was considered in those patients with persisting hypotension requiring vasopressors despite adequate resuscitation.

Higher severity was considered when children met one or more of the following criteria: death, sequelae, admission to the intensive care unit (ICU), sepsis, meningitis and/or acute complications including renal or hepatic failure, stroke, acute respiratory distress syndrome or catheter replacement.

We created two forms to be completed online using Google Drive application (Google LLC). Questionnaires were initially distributed to all participating EDs seeking to ensure the clarity of the methods and to enhance the quality of the data collected and were fulfilled by the site investigators. The first questionnaire was a patient registration form for each positive blood culture collected, with epidemiological and clinical data, the results of tests performed, final diagnosis and outcome. A second form was used to provide the following additional, monthly data: total number of patients attended, of blood cultures taken and of positive blood cultures obtained.

Only the research coordinator had access to the two resulting online databases, being responsible for downloading regular backups of both databases and reviewing them for possible errors in data

entry. The participating researcher in each centre was responsible for reviewing the episodes with potential errors.

To identify types of *E coli* bacteraemia presentations, we used multiple correspondence analysis and cluster analysis. In order to perform multiple correspondence analyses,[9] we used the following categorical variables: sex, age, PAT, previously healthy, fever, other symptoms and physical examination. Age was categorised into <3 months, 3-12 months and >12 months; PAT into normal, altered appearance, altered circulation to the skin and altered work of breathing. We then performed the cluster analysis, which organises information from apparently heterogeneous episodes into relatively homogenous groups. We used the factors obtained in the multiple correspondence analyses as variables to perform the cluster analysis and to obtain the appropriate grouping of *E coli* bacteraemia presentations.[10] To create clusters, we used the squared euclidean distance and Ward method.[11] This method combined correspondence analysis and cluster analysis to categorise *E coli* bacteraemia cases into groups. These groups were suggested by the data and not defined a priori. The groups were made in a way such that cases in a given group of *E coli* bacteraemia were similar to each other and those in different groups were dissimilar.

Finally, chi-square test was used to study the association between severity and different types of *E coli* bacteraemia presentations. Outcome measure was the presence of, at least one of the severity criteria described previously.

We performed all statistical analyses using SPSS vs. 23.0 statistical software and R project, version 3.6.2 'Dark and Stormy Night' (IBM).

This study was approved by the Ethical Committee of the Basque Country (registration number PI2011040). Approval for the study and for data sharing with the coordinating institution and with the centralised data centre was granted by the institutional review board at each participating institution. To maintain patient confidentiality, the forms did not include any data that would have allowed the identification of any patient.

3 | RESULTS

During the time of the study, we registered a total of 3 936 827 ED episodes, of which a positive blood culture was isolated in 1696 (0.04%, CI 95% 0.04-0.05). In 291 (17.6%, 95% CI 15.4-19.0), blood culture was positive for *E coli*. Table 1 reports descriptive statistics for the main epidemiological variables, management and outcome of the children with *E coli* bacteraemia.

Final diagnosis were UTI with associated bacteraemia 206 (70.8%); occult bacteraemia 27 (9.3%); sepsis/shock 32 (11%, three of them with associated meningitis); meningitis 5 (1.7%); catheter-associated bloodstream infection 6 (2.1%); and others 15 (5.1%). Of the 291 patients, 43 (14.8%, 95% CI 11.2-19.3) were considered to have severe illness (Table 2). Two patients died.

The multiple correspondence analyses rand cluster analysis identified four main types of paediatric *E coli* bacteraemia presentations (Table 3). Two types of *E coli* bacteraemia presentations (groups A and B) were mainly related to well-appearing previously healthy infants <12 months old with associated UTI (85.0% and 98.5%,

TABLE 1 Epidemiological and clinical characteristics, complementary tests, management and disposition of the patients with *E coli* bacteraemia

Age (in months)[a]	3 (1-11)
Sex (female)	131 (45%)
Non- previously healthy patients	67 (23%)
Immunosuppression	27 (9.3%)
Patients with multiorgan syndromes or systemic illness	16 (5.4%)
Serious kidney or urinary malformations[b]	13 (4.5%)
Presence of a mechanical device	7 (2.4%)
Invasive diagnostic or therapeutic procedure in the previous 10 d	4 (1.4%)
Duration of the fever (in hours)[a]	12 (3-24)
Temperature upon arrival to the emergency department (°C)[c]	37.9 ± 1.0
Well appearing upon arrival to the emergency department	244 (83.8%)
No findings in the physical examination	226 (77.7%)
Urine culture performed	263 (90.4%)
Lumbar puncture performed	71 (24.4%)
Chest X-ray performed	33 (11.3%)
Administered antibiotic	284 (97.6%)
Admission to ward/Intensive care unit	255 (87.6%)

Note: Data are expressed as n and percentage.

[a]Age and evolution time are expressed as median and interquartile range.

[b]Serious kidney or urinary malformations: double renal system, severe bilateral vesicoureteral reflux and presence of ureterostomy or vesicostomy.

[c]Temperature is expressed as mean ± standard deviation.

respectively, compared with 50% and 30.2% of groups C and D). The main differences between groups A and B were the age and the sex, but, overall, they did well. Group A included mostly males younger than 3 months of age (81.4%) and group B mainly females (87.7%) 3-12 months old. Rate of severity was 5.3% and 3.1%, respectively.

Well-appearing children older than 12 months with underlying diseases accounted for the majority of the third group of patients (group C). The last group (group D) included non-well-appearing children of different ages, one-third of them non-previously healthy. Associated UTI was significantly lower in these two groups (group C = 50.0%, group D = 30.2%), and the rate of severity was 15% and 50.9%, respectively (significantly higher than in groups A and B, $P < .01$). The two patients who died were included in group D.

Eight children were diagnosed with bacterial meningitis (three of them with associated sepsis). All of them were younger than 5 months. The rate of associated meningitis in febrile infants with *E coli* bacteraemia is shown in Table 4.

TABLE 2 Number of patients with each severity criteria

Severity criteria	N (%)
Sepsis	32 (11.0)
Admission to the intensive care unit[a]	22 (7.6)
Acute complications	8 (2.7)
Meningitis	8 (2.7)
Sequelae	7 (2.4)
Death	2 (0.7)

Note: Data are expressed as n and percentage. Twenty patients (6.9%) presented a single severity criteria.

Sixteen patients (5.5%) presented two severity criteria.

Seven patients (2.4%) presented three or more severity criteria.

[a]There is no patient with this severity criteria exclusively.

4 | DISCUSSION

Our data suggest four different types of paediatric *E coli* bacteraemia presentations to the ED with different degree of severity. Association with UTI in children less than a year was most common, whereas older age was associated with greater severity, mainly when the child was unwell upon presentation to the ED.

Many children did not have high fever and abnormal findings in the physical examination were uncommon. In addition, the majority of these children appeared well when evaluated in the ED. This underlines the importance of having a high index of suspicion in selected patients.

E coli is the most common pathogen involved in invasive bacterial infections in young febrile infants.[3,5] Many of these are associated with UTI, which is the most common serious bacterial infection in young febrile infants.[12] Young febrile infants with UTI are more prone to have associated bacteraemia.[12] Around 5% of febrile infants <3 months of age with UTI have an associated bacteraemia, with the highest risk in infants <28 days.[13] Traditionally, it has been recommended to hospitalise young febrile infants with suspected UTI due to the concern of acute adverse events and for missing concomitant bacteraemia. During the last years, efforts have been made to identify young febrile infants <3 months with suspected UTI at low risk for bacteraemia and suitable for outpatient management.[14,15] Several studies have assessed the course of febrile infants with UTIs and suggest that otherwise well-appearing infants with or without concomitant bacteraemia have benign clinical outcomes when treated with appropriate antibiotics.[16-18] Our study may support a less conservative management. In fact, in our study, only around 5% of febrile infants with *E coli* bacteraemia had a severe disease, including those <3 months of age. Nevertheless, all except one of the children with bacterial meningitis were younger than two months of age. Nearly 10% of

TABLE 3 Main types of paediatric *E coli* bacteraemia presentations

Variable		A (n = 113, 38.8%)	B (n = 65, 22.3%)	C (n = 60, 20.6%)	D (n = 53, 18.2%)	*P* value
Sex	Female	21 (18.6%)	57 (87.7%)	36 (60%)	17 (32.1%)	<.001
Age	<3 mo	95 (84.1%)	10 (15.4%)	3 (5%)	24 (45.3%)	<.001
	3-12 mo	18 (15.9%)	55 (84.6%)	6 (10%)	15 (28.3%)	
	>12 mo	0	0	51 (85%)	14 (26.4%)	
Previously healthy	No	3 (2.7%)	0	47 (78.3%)	17 (32.1%)	<.001
Fever[a]	Yes	88 (77.9%)	65 (100%)	58 (96.7%)	41 (77.4%)	<.001
Other symptoms	Yes	24 (21.2%)	40 (61.5%)	30 (50%)	45 (84.9%)	<.001
Paediatric assessment Triangle	Altered appearance	1 (0.9%)	1 (1.5%)	2 (3.3%)	35 (66%)	<.001
	Altered circulation	1 (0.9%)	0	1 (1.7%)	18 (34%)	
	Altered breathing	0	0	0	6 (11.3%)	
Physical examination	Altered	7 (6.2%)	5 (7.7%)	8 (13.3%)	45 (84.9%)	<.001
Associated UTI	Yes	96 (85%)	64 (98.5%)	30 (50%)	16 (30.2%)	<.001

Note: Data are expressed as n and %. The *P* values demonstrate the differences between groups among the analysed variables.

[a]Temperature higher than 38°C at home and/or at the emergency department.

TABLE 4 Rate of associated meningitis in febrile infants with *E coli* bacteraemia related to the age

Group of age	Rate of bacterial meningitis
<1 mo old	6/64, 9.4%, 95% CI 4.4-19
1 mo old	1/38, 2.6%, 95% CI 0.5-13.5
2 mo old	0/30, 0, 95% CI 0-11.3
3-24 mo old	1/107, 0.9%, 95% CI 0.2-5.1

Note: Data are expressed as n, percentage and confidence interval.
Abbreviation: CI, confidence interval.

febrile infants younger than 1 month old with *E coli* bacteraemia had associated bacterial meningitis. Higher risk of meningitis associated UTI has been previously published in febrile neonates.[16] Our study supports the decision of making a cerebrospinal fluid examination in febrile neonates with confirmed or suspected *E coli* bacteraemia.[15]

Although the diagnosis of bacterial meningitis is very rare in older children with *E coli* bacteraemia, severe illness is more common in these patients. In our series, around 50% of non-well-appearing children with *E coli* bacteraemia had a severe disease, including two children who finally died. This emphasises the importance to consider UTI in those non-well-appearing febrile children and, if possible, to collect a urine culture before initiating the antibiotics. This also confirms that PAT is a reliable tool to identify children with severe illness upon the arrival to the ED.[7]

Finally, the group of older febrile children with underlying diseases had a 15% rate of severe disease. This underscores the importance of a more cautious management of children with underlying diseases because of the high risk of invasive infections when these children present to the ED.[19,20]

Our study shows certain limitations. Our registry was not designed to characterise the ED presentations of paediatric *E coli* bacteraemia. Nevertheless, we think that collected data allow us to define the different types of these presentations and to relate them with severity. This study was conducted to identify risk factors in children with *E coli* bacteraemia and not UTI. In addition, *E coli* is not the single pathogen responsible for UTI especially in children with underlying diseases. Thus, our results cannot be extrapolated to febrile UTI. Finally, we think that defining the indications for cerebrospinal fluid examination would require a specific larger study. Nevertheless, our data support to strongly consider cerebrospinal fluid examination in infants <2 months old with *E coli* bacteraemia.

5 | CONCLUSION

We conclude that there are four different types of paediatric *E coli* bacteraemia presentations to the ED with different rate of severity. UTI-associated bacteraemia in infants <12 months were most common but those involving older children account for large amount of patients and are related to higher risk, mainly when the child is unwell upon the arrival to the ED. Associated bacterial meningitis is rare in children older than two months of age.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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Markers for invasive bacterial infections in previously healthy children

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1. Introduction

Most previously healthy febrile children have self-limited viral infections. However, sometimes, fever is due to an invasive bacterial infection (IBI). Prompt identification of these children is essential to initiate an early and appropriate treatment. Nevertheless, this identification may be difficult. In a recent study, 22% of children with bacterial meningitis or sepsis had repeated emergency department (ED) visits before admission [1]. Currently, these children are often brought very early to the ED, and signs and symptoms of children with an IBI can be difficult to distinguish from self-limited febrile illnesses [2]. Furthermore, most of these patients are younger than 2–3 years-old, being the clinical expression of different infections more unspecific.

Therefore, physicians may not be confident enough in the physical exam and seek for blood tests like white blood cell count (WBC) or the absolute neutrophil count (ANC) to guide initial clinical decision-making in certain febrile children. In the last decades, C-reactive protein (CRP) and procalcitonin (PCT) have emerged as valuable risk-stratification tests to identify high-risk infants [3]. To analyze the response of blood biomarkers commonly used in the ED in children with microbiologically confirmed IBIs seems important.

Our hypothesis is that the response of the blood tests to IBI varies related to the causative pathogens and the final diagnosis.

The objective of the study is to analyze the markers' profile in previously healthy children when evaluated in the ED and finally diagnosed with an IBI: WBC, ANC, CRP and PCT.

2. Patients and method

This was a retrospective, descriptive study based on a registry of a cohort of children under 14-years-old microbiologically diagnosed with an IBI in a pediatric ED of a tertiary teaching hospital in Spain between January 2008 and May 2020.

We identified patients with IBI from the hospital's electronic records as we have previously described [4]. We obtained the information of the patients from the electronic clinical records of the pediatric ED and Basque Public Health System, including socio-demographic data, personal history, month and year of consultation, pneumococcal and meningococcal vaccination status, duration of fever, associated symptoms, maximum temperature, previous consultation in the ED, appearance upon arrival, physical exam, performed tests, microorganism isolated, final diagnosis, disposition and evolution of the patient. We included these data in the registry of IBI in the month after the visit to the ED.

For the purpose of this subanalysis, we included those children classified as previously healthy patients and excluded those non-previously healthy: immunosuppression (oncological illness, chronic renal failure, transplant patient, sickle cell disease); presence of a mechanical device (indwelling catheter, ventriculoperitoneal shunt, auditory prostheses); and chronic diseases/severe malformative syndromes.

2.1. Definitions

Invasive bacterial infection (IBI): isolation in blood or cerebrospinal fluid (CSF) of a bacterial pathogen, using bacterial culture or real time polymerase chain reaction (PCR) technique to detect *S. pneumoniae* and *N. meningitidis*.

Fever without a source (FWS): axillary or rectal temperature higher than 38 °C registered at home or in the ED, without associated respiratory symptoms, diarrhea process and findings on physical examination that allows identifying the source of the fever.

Occult bacteremia (OB): presence of a pathogenic bacterium in the blood of a well-appearing febrile child in the absence of an identifiable focus of infection.

Sepsis: based on the criteria published by Goldstein et al., with the following adjustment: well-appearing patients with fever and leukocytosis were not diagnosed with sepsis unless they had another added criterion (tachycardia, bradycardia, tachypnea or signs of organ dysfunction). [5]

Normal blood tests values: in accordance with the most accepted limits, we considered the following normal values: WBC between 5000 and 15,000/mm^3, ANC between 1500 and 10,000/mm^3, CRP less than 20 mg/L, PCT less than 0.5 ng/mL.

Well-appearing patients: patients with a stable pediatric assessment triangle [6] upon arrival at the ED.

2.2. Statistical analysis

We performed the statistical analysis using the IBM SPSS Statistics for Windows, version 23.0 (IBM, Armonk, New York, USA).

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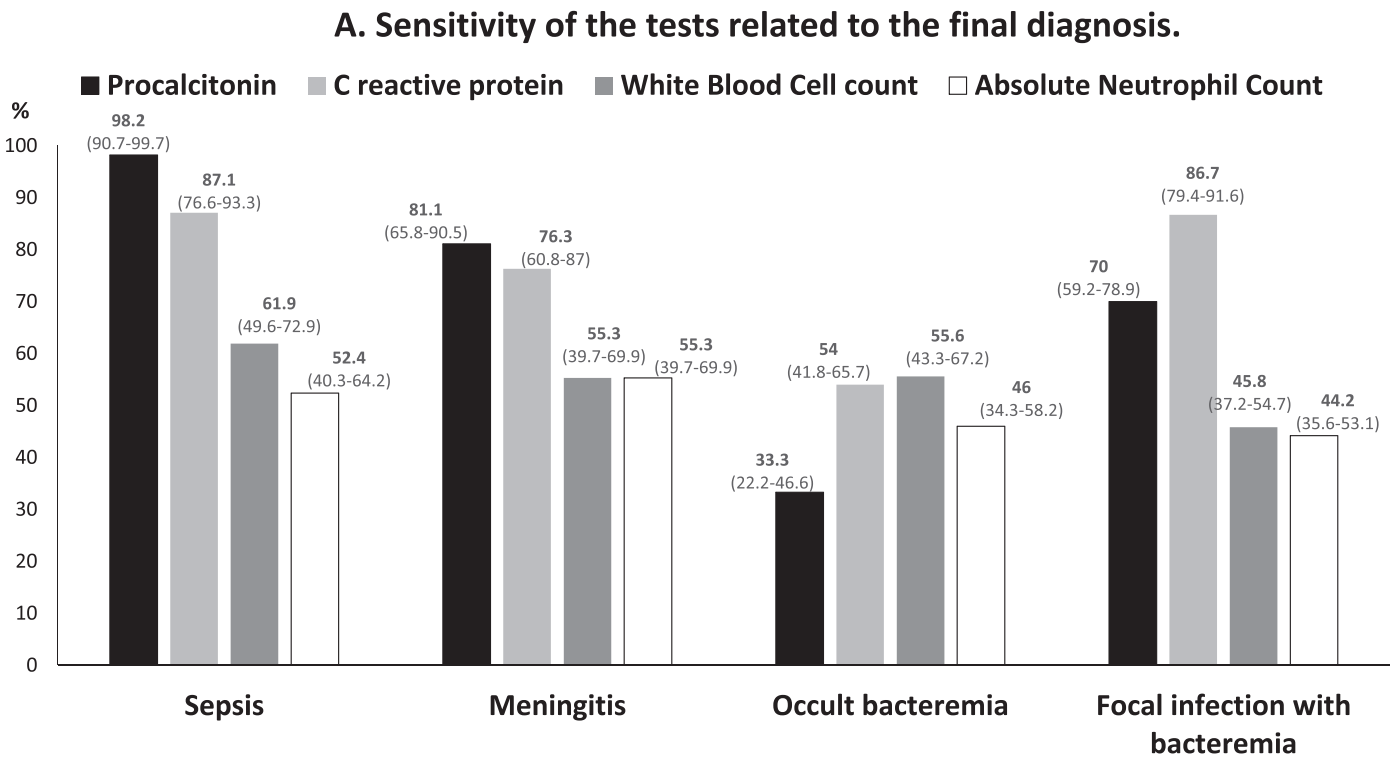

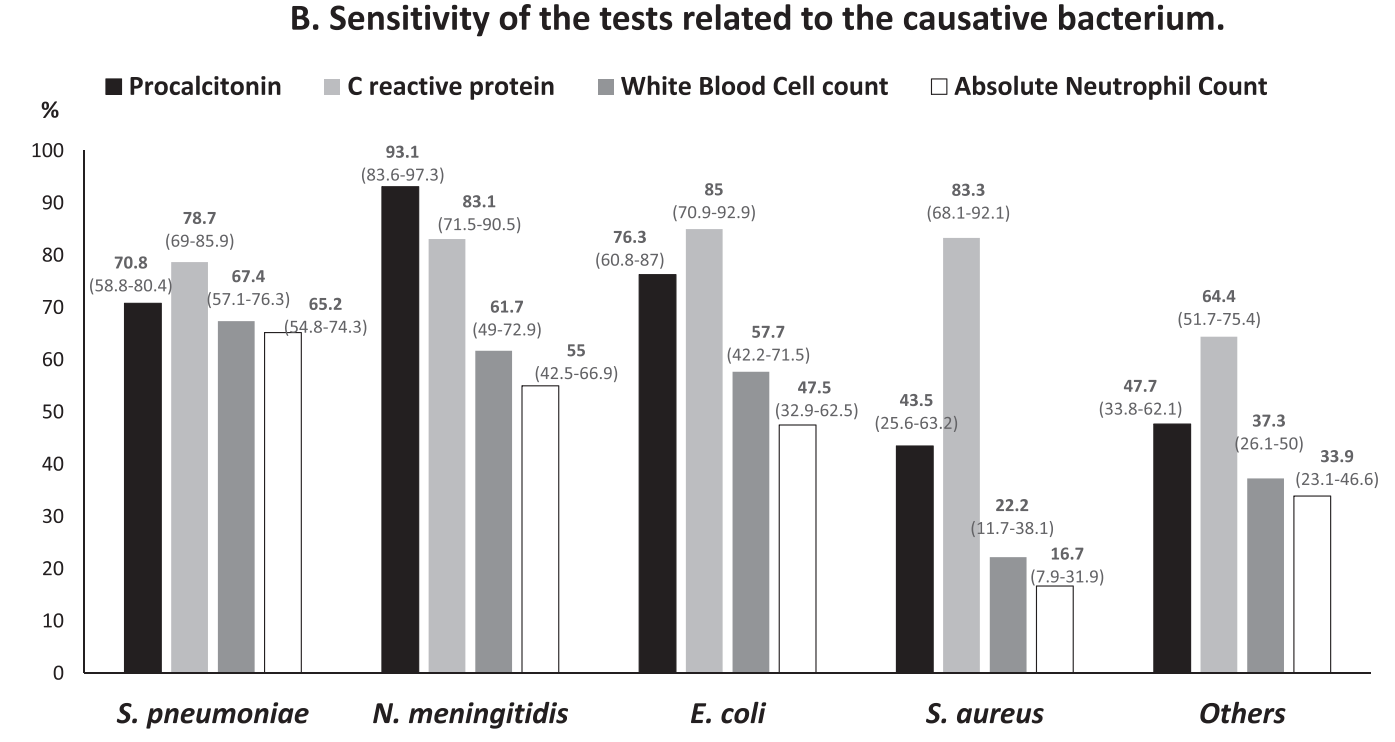

Rate of patients with procalcitonin >0.5 ng/mL, C reactive protein>20 mg/L, white blood cell count less than 5000 or higher than 15000/mm^3; absolute Neutrophil Count less than 1,500 or higher than 10,000/mm^3. 95% Confidence intervals in brackets.

Fig. 1. Profile of white blood cell count, absolute neutrophil count, C-reactive protein and procalcitonin in invasive bacterial infections.

We calculated the sensitivity of each blood test commonly used in the ED (WBC, ANC, CRP and PCT) for identifying an IBI. To identify variations in the markers' profile of each IBI and according to the causing bacterium, we also calculated the sensitivity of aforementioned markers for the different IBIs diagnosed.

The Clinical Research Ethics Committee of the Hospital approved the study (Code E11/52).

3. Results

During the study period, we registered 665.997 episodes in the pediatric ED, of which 367 (0.05%) were finally diagnosed with an IBI. Of these, 286 (77.9%) were previously healthy and were included in the study. One hundred and sixty (55.9%) were male, median age was 14 months (interquartile range 5–42), 107 (37.4%) had received two or more doses of pneumococcal conjugated vaccine (PCV) and 8 (2.8%) B meningococcal vaccine. Two hundred (69.9%) were well appearing and, of these, 95 had a normal physical exam. Final diagnoses were sepsis 64 (22.4%), meningitis 38 (13.3%), OB 63 (22.0%), focal infection with bacteremia 121 (42.3%) (respiratory tract infection 46, urinary tract infection 33, osteoarticular or soft tissue infection 33, and others 9). Isolated bacteria were *Streptococcus pneumoniae* 89 (31.1%), *Neisseria meningitidis* 61 (21.3%), *Escherichia coli* 40 (14.0%), *Staphylococcus aureus* 36 (12.6%), others 60 (21.0%). Two hundred and ten patients (73.4%) received antibiotics on the first visit to the ED, 3 died and 14 showed sequelae.

WBC and ANC were performed in 284 patients (99.3%), CRP in 283 (99.0%) and PCT in 228 (79.7%). Most patients without PCT were attended in the first two years of the study (phase of introduction of the PCT in our department) or were diagnosed with a pneumonia. Overall, 265 (92.7%) had, at least, one altered test. The sensitivity of each test was as follows: PCT 70.1% (CI 95% 63.9–76.0), CRP 78.1% (CI 95% 72.9–82.5), WBC 52.8% (CI 95% 47.0–58.6) and ANC 47.9% (CI 95% 42.1–53.7). Additionally, 85.2% (CI 95% 78.7–90) of the altered WBC count were leukocytosis and 99.5% (CI 95% 97.1–100) of the altered ANC were neutrophilia. Leukopenia was an uncommon finding except in patients with sepsis [22.2% (95% CI 13.7–33.9)].

The sensitivity of the blood tests varied related with the final diagnosis and the causing bacterium (Fig. 1).

Among those 89 patients in whom *S. pneumoniae* was isolated, 40 (44.9%) received at least two doses of pneumococcal conjugated vaccine. The accuracy of the markers did not vary related to the vaccination status. Twenty-nine febrile infants between 3 and 24 months of age were diagnosed with a pneumococcal OB. Of these, sensitivity of each marker was: PCT 43.5% (CI 95% 25.6–63.2); CRP 48.3% (CI 95% 31.4–65.6); WBC count 75.9% (CI 95% 57.8–87.8); ANC 58.6% (CI 95% 40.7–74.5).

Overall, 21 patients (7.3%) showed no alteration of any blood test. The median of age of these patients was 2 months (IQR 1–11 months) and, except for two, all of them were well-appearing. Final diagnosis were occult bacteremia 11 (52.4%), meningitis 4 (19%), and other focal infections 6 (28.6%). Six (28.6%) were started on antibiotics despite normal values of the blood tests (vs 242 of 261 patients, 92.7% of those with at least, one altered blood test; $p < 0.001$). All of them did well.

Globally, seventy-six patients (26.6%) had a previous visit to the ED and antibiotics were not started on that visit. Except for two, all of them were well-appearing on the first visit, median age and sex distribution was similar to the whole sample and most common diagnoses were fever without a source or upper respiratory tract infection (56, 73.7%). Two of these patients finally died and eight had sequelae (mainly neurological and osteoarticular sequelae).

4. Discussion

Most previously healthy febrile children with a microbiologically confirmed IBI show alterations of, at least, one of the blood tests commonly used in the ED. Nevertheless, it should be noted that the sensitivity of these markers varied related to the isolated causative bacterium and the final diagnosis of the patient. Overall, PCT and CRP appear more frequently altered than classic markers, mainly in children with severe disease like sepsis or meningitis, being their performance quite poor in children with occult bacteremia.

Identifying febrile children with an IBI when evaluated at the ED remains challenging and, initially, depends on recognizing clinical signs and symptoms. Most algorithms are based on abnormal selected vital parameters and level of consciousness. But, in a large proportion of children with fever due to self-limiting infections vital signs may be abnormal [7]. In addition, children are often able to maintain normal haemodynamic parameters in the early stages of sepsis. Thus, it is comprehensible to use blood tests in some situations to rule in or rule out an IBI.

In recent decades, new biomarkers, such as CRP and PCT, have been added to screening tests in febrile children. Our results confirm that, globally, CRP and PCT levels provide the most diagnostic value in feverish children to detect those with serious bacterial infection [3]. Furthermore, PCT offers some advantages in order to identify patients with IBI [8], including meningitis [9] and invasive meningococcal disease. CRP appears more useful when evaluating children with suspected focal infections with associated bacteremia, mainly soft tissue and osteoarticular infections due to *Staphylococcus aureus*. Children with occult bacteremia deserve special attention. These infants appear well and lack an identifiable focal bacterial source of infection. PCT is not very useful when evaluating febrile infants at risk for pneumococcal OB as it has previously been reported with CRP [10]. In these children, the sensitivity of classic markers, mainly WBC, is higher.

Finally, it should be underlined that adding more blood tests when evaluating febrile children may increase the number of patients who receive antibiotics instead of selecting better those who should receive them [11].

Our study has certain limitations. The data were collected retrospectively. Even so, all patients admitted in our pediatric ED are recorded electronically, including medical histories and notes concerning progression and follow-up of them. This makes the collection process consistent. On the other hand, this was not a multicenter study and, therefore, our results should be cautiously extrapolated to other settings. Finally, those febrile children with no identified pathogen in blood or CSF were not included in the study. This should have let us establishing the specificity and the predictive values of the different blood tests, providing a better accuracy of blood tests when evaluating these children in the ED.

Most previously healthy febrile children with an IBI show alterations of blood tests commonly obtained when evaluated in the ED. The response of these tests varies related to the isolated causative bacterium and the final diagnosis. This should be considered when tests are used to guide initial clinical decision-making in certain clinical scenarios.

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Ethics

Approved by The Clinical Research Ethics Committee of the Basque Country (internal code E11/52).

Author statement

Dr. Gangoiti conceptualized and designed the study, supervised data collection, analyzed the data, wrote the initial draft of the manuscript, and approved the final manuscript as submitted.

Dr. Fernandez collaborated in the design of the data collection system and critically revised the manuscript.

Dr. Gallego collaborated in the design of the study and critically revised the manuscript.

Dr. Gomez collaborated in the design of the study and critically revised the manuscript.

Dr. Benito reviewed the design of study and critically revised the manuscript.

Dr. Mintegi collaborated in the design of the study, supervised data collection, analyzed the data, revised the initial draft of the manuscript, and approved the final manuscript as submitted.

All of them approved the final manuscript as submitted.

Declaration of competing interest

The authors have no conflicts of interest to disclose.

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DISCUSSION

Several studies describe the effect of coronavirus disease in gastrointestinal system. Liver damage, expressed as elevation in liver aminotransferase levels, has been reported and diverse pathophysiologic mechanism has been proposed. Severe disease has been associated with higher rates of liver dysfunction.[1–3]

Prevalence rates of preexisting liver disease in COVID-19 adult patients vary from 3% to 11%. However, in pediatric population liver disease is rare. Several studies have identified significant risk factors for the severity of COVID-19 disease. Moreover, drug hepatotoxicity has been reported as a cause of liver impairment in patients with COVID-19. Many of the medications used for SARS-CoV-2 infection, such as antivirals, antibiotics, acetaminophen, and nonsteroidal anti-inflammatory drugs, are potentially hepatotoxic.[4] In critically ill COVID-19 patients, hepatic injury may be caused by changes in hemodynamics and oxygen delivery. In acute cardiovascular or respiratory failure, systemic arterial pressure suddenly declines, leading to a reduction in hepatic arterial perfusion, and hepatocellular hypoxia. Hypoxic hepatitis is associated with a sharp increase in LFTs.

SARS-CoV-2 engages the angiotensin-converting enzyme 2 as the entry receptor on host cells and uses the transmembrane protease serine 2 (TMPRSS2) for S protein priming.[5] Significant enrichment of angiotensin-converting enzyme 2 expression has been found in a major portion of the cholangiocytes and lower in hepatocytes, providing a theoretical basis for liver injury in COVID-19 infection. In addition to this, pathologic studies have illustrated the presence of the SARS-CoV-2 in postmortem liver biopsies of COVID-19 patients with liver enzyme abnormalities, contrary to previous studies that did not manage to identify the virus in liver tissue.[6] Wang et al demonstrated the presence of amounts of typical coronavirus particles in cytoplasm of hepatocytes in 2 patients.[7] The above support the hypothesis of direct SARS-CoV-2 infection in the liver, causing cytopathy of hepatocytes and impaired liver function.

Our 5-year-old patient was a previously healthy child, who had been heavily exposed to SARS-CoV-2. Preexisting liver disease or other comorbidities were absent. He had not been exposed to medications, before admission to pediatric department or during his hospitalization, remaining hemodynamically stable. His clinical phenotype with nausea and vomiting, in conduction with increased LFTs and inflammatory markers, in the absence of the above risk factors, supports the infectious cause of liver injury. The course of his disease was short, and the patient had a complete clinical recovery, with normalization of laboratory profile.

False negative results of RT-PCR testing for SARS-CoV-2 have been reported in several previous studies. A systematic review that included 34 studies, enrolling 12.057 COVID-19 patients, reported 1060 cases with RT-PCR negative findings in their initial assessment.[8] In the same article is stated that up to 54% of COVID-19 patients may have an initial negative RT-PCR result. Xiao et al found that 23.3% of 301 patients who had 3 consecutive SARS-CoV-2 RT-PCR assays in first 2 tests they had negative results. The median period between onset of symptoms and positive SARS-CoV-2 RT-PCR test result was 16 days (IQR, 10–23).[9] Another study that Yafang Li et al conducted, including 610 hospitalized patients from Wuhan, demonstrated that in the first test, 63.0% of COVID-19 were negative. Among them, in the second test, 72.9% remained negative. Among the patients with initial nonpositive results, 7 patients were eventually confirmed with COVID-19 by 3 repeated swab PCR tests, 4 were confirmed by 4 repeated tests, and 1 was confirmed by 5 repeated tests.[10] Our patient had been subjected to SARS-CoV-2 RT-PCR test with specimens from nasal swabs twice, initially at symptoms onset and later on the 9th day of the disease, and the results were negative in both of the tests. On the 16th day of the disease, he was tested for SARS-CoV-2 IgG antibodies with positive results in high titer.

CONCLUSION

The case details an unusual presentation of COVID-19 disease in children. The patient presented a mild clinical phenotype of the disease, affecting the gastrointestinal system, but greatly elevated liver enzymes, indicative of severe liver injure that was directly attributed to SARS-CoV-2. Although favorable prognosis of COVID-19 infection in children has been reported in many studies, clinicians need to be aware of this disease expression to ensure prompt recognition.

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REPEATED EMERGENCY DEPARTMENT VISITS AMONG CHILDREN WITH INVASIVE BACTERIAL INFECTIONS

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Abstract: We carried out a retrospective cohort study of 271 previously healthy children younger than 14 years old diagnosed with invasive bacterial infection in an emergency department. Of them, 72 (26.6%) had previous visits to the emergency department. Not identifying children with an invasive bacterial infection and not administering antibiotics on the first visit was associated with a severe outcome.

Key Words: antibiotic treatment, invasive infection, outcome, revisit

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Fever is one of the main reasons for consultation among children attending the emergency department (ED). Most cases correspond to self-limiting viral infections. The rate of invasive bacterial infections (IBIs) has declined significantly after the introduction of the conjugate vaccines. However, they are still a major cause of death in developed countries.[1]

Early identification of children with IBI may be difficult. Children are often brought to the ED after only a few hours of fever and children with an IBI can be difficult to distinguish from those with self-limited febrile illnesses. In addition, most children with IBI are younger than 2–3 years old, and in these patients, the manifestations of many infectious diseases are usually unspecific.[2] In a recent study, 22% of children with bacterial meningitis or sepsis had repeated ED visits before admission, yet they had health outcomes similar to those of children admitted on initial visit.[3] Nevertheless, pediatric sepsis management guidelines recommend administration of intravenous antimicrobials be initiated as soon as possible after recognition and within 1 hour for both sepsis and septic shock.[4] In a previous article,[5] we identified duration of fever less than 24 hours, symptoms other than fever and not being well-appearing upon arrival to the ED to be independent risk factors for greater severity. Nevertheless, previous ED visits were not considered.

We hypothesize that not administering parenteral antibiotics on the initial visit to the ED is related to severe outcome in pediatric IBIs.

The objective of the study was to evaluate the impact of not administering parenteral antibiotics on initial visit to the ED on the outcome of children with an IBI.

PATIENTS AND METHODS

We conducted a retrospective registry-based cohort study that included all the previously healthy children less than 14 years old diagnosed with an IBI in a pediatric ED between 2008 and 2019. Our ED is a tertiary teaching hospital with around 55,000 episodes/year corresponding to children younger than 14 years of age.

Definitions

IBI is defined as the identification of bacterial pathogen in blood and/or cerebrospinal fluid by growth in bacterial culture and/or genomic detection of *Neisseria meningitidis* or *Streptococcus pneumoniae* by real-time quantitative polymerase chain reaction (q-PCR) technique.

Severe outcome is defined as patient who died or had permanent sequelae identified in the following 12 months after the IBI. Sequelae were defined as a morbid condition following or occurring as a consequence of the IBI.

Well-appearing patients are defined as those with a stable pediatric assessment triangle upon arrival at the ED.

Nonpreviously healthy patients are those with immunosuppression (oncological illness, chronic renal failure, transplant patient, sickle cell disease); presence of a mechanical device (indwelling catheter, ventriculoperitoneal shunt, auditory prostheses) and chronic diseases/severe malformative syndromes.

Sepsis is defined as that based on the criteria published by Goldstein et al,[6] with the following adjustment: well-appearing patients with fever and leukocytosis were not diagnosed with sepsis unless they had another added criteria (tachycardia, bradycardia, tachypnea or signs of organ dysfunction).

Meningitis is defined as the identification of bacterial pathogen in cerebrospinal fluid by growth in bacterial culture and/or genomic detection of *N. meningitidis* or *S. pneumoniae* by q-PCR technique; or pleocytosis with identification of bacterial pathogen in blood by culture or q-PCR technique.

Patient Identification

Patients with IBI were identified from the hospital's electronic records as it has been previously described.[5] Sequelae were addressed reviewing medical electronic records of the children in the following 12 months after the IBI.

Nonpreviously healthy patients were excluded.

We carried out the statistical analysis using the statistical program IBM SPSS Statistics for Windows Version 23.0 (Armonk, NY). The qualitative variables were described using absolute frequencies and percentages, and the continuous variables were described using both the mean and standard deviation or median and interquartile range. The χ^2 test was used to study the association between qualitative variables.

The Clinical Research Ethics Committee of the Hospital approved the study (Code E11/52).

RESULTS

During the study period, we registered 601,902 episodes in the ED, corresponding to children less than 14 years old. Of these, 342 were diagnosed with an IBI. Seventy-one were excluded. Seventy (20.5%) were not previously healthy: immunosuppression (41; 12%), mechanical device (15; 4.4%) chronic diseases or complex syndromes (14; 4.1%). Another one was excluded because he died before reaching the ED (sepsis due to *S. pyogenes*).

Finally, we included 271 previously healthy children less than 14 years old diagnosed with an IBI. Median age was 15 months old (interquartile range 5–43 months old; of them 18 younger than 1-month-old and 34 between 1 and 3 months of age) and 118 (43.5%) were female. One-hundred ninety-nine patients (73.4%) received parenteral antibiotic on first visit and 72 (26.6%) did not (Table 1). Median of time between the first and second visit in those patients who did not receive parenteral antibiotic was 36 hours (interquartile range 24–48 hours). Fifteen patients had severe outcome, including 3 deaths and 12 patients who developed sequelae: neurologic 5 (replacement of ventriculoperitoneal device, hydrocephalus, deafness and epilepsy), 3 osteoarticular (need for a prosthesis, permanent limp and small amputations), 2 chronic renal failure (one of them requiring kidney transplant), 2 chronic restrictive respiratory problems and 1 cardiologic sequelae (multiple valve replacements). Seven of the 15 patients with severe outcome did not receive antibiotic on the first visit (2 deaths, 5 sequelae).

The rate of severe outcome varied related to the type of IBI: sepsis 9 of 61 (14.8%; 95% confidence interval [CI], 7–26.2), meningitis 3 of 36 (8.3%; 95% CI, 1.7–22.5), occult bacteremia 0 and focal infection with bacteremia 3 of 119 (2.5%; 95% CI, 0.5–7.2). The rate of severe outcome did not vary related to the time interval between the initial and return visit (3 of the 29 children who had an ED visit in the preceding 24 hours had severe outcome, 10.3%; vs 4 of the 40 children who returned to the ED within more than 24 hours, 10%, $P = 1$).

TABLE 1. Characteristics of Previously Healthy Patients With an Invasive Bacterial Infection in Relation to the Administration or Nonadministration of Parenteral Antibiotic on the First Visit to the Emergency Department

Characteristics	Parenteral Antibiotic Administered in the First ED Visit		
	Yes (n = 199)	No (n = 72)	*P*
Age (mo)	15 (5–43)	14 (4–42)	NS
Sex (female)	87 (43.7%)	31 (43.1%)	NS
Season			<0.01
Spring	33 (16.6%)	21 (29.2%)	
Summer	31 (15.6%)	16 (22.2%)	
Autumn	68 (34.2%)	19 (26.4%)	
Winter	67 (34.2%)	16 (22.2%)	
Fever: yes	195 (98%)	59 (81.9%)	<0.01
Duration of fever (h)	12 (5–32)	12 (8–48)	NS
Not well-appearing upon the arrival to the ED	56 (28.1%)	2 (2.8%)	<0.01
No other symptom except fever	58 (29.1%)	33 (45.9%)	0.01
Digestive	44 (22.1%)	11 (15.3%)	
Respiratory tract and ORL	37 (18.6%)	18 (25%)	
Neurological	37 (18.6%)	3 (4.2%)	
Exanthema	22 (11.1%)	2 (2.8%)	
Joint/soft tissue	17 (8.5%)	7 (9.7%)	
Normal physical examination	72 (36.2%)	51 (70.8%)	<0.01
Other signs			
Exanthema	50 (25.1%)	6 (8.3%)	
Neurological	38 (19.1%)	2 (2.8%)	
Respiratory tract and ORL	28 (14.1%)	11 (15.3%)	
Joint/soft tissue	17 (8.5%)	2 (2.8%)	
Isolated microorganism			NS
Streptococcus pneumoniae	60 (30.2%)	24 (33.3%)	
Neisseria meningitidis	47 (23.6%)	10 (13.9%)	
Staphylococcus aureus	20 (10.1%)	14 (19.4%)	
Escherichia coli	31 (15.5%)	7 (9.7%)	
S. agalactiae	11 (5.5%)	1 (1.4%)	
Others	30 (15.1%)	17 (22.3%)	
Final diagnosis			NS
Sepsis	47 (23.6%)	14 (19.4%)	
Meningitis	28 (14.1%)	8 (11.1%)	
Occult bacteremia	36 (18.1%)	19 (26.4%)	
Focal infection with bacteremia	88 (44.2%)	31 (43.1%)	
Urinary tract infection	28 (14.1%)	4 (5.6%)	
Pneumonia	24 (12.1%)	8 (11.1%)	
Osteoarticular or soft tissue infection	19 (9.5%)	12 (16.7%	
Others	17 (8.5%)	7 (9.7%)	
Severe outcome	8 (4%)	7 (9.7%)	0.07

NS indicates not significant; ORL, otorhinolaryngological.

Data expressed as n (%) except for age and duration of fever (median and interquartile range).

DISCUSSION

A significant percentage of previously healthy children with an IBI are not identified on their first visit to the ED. Failure to identify IBI and not initiating antibiotic on first visit is associated with higher mortality and sequelae rate. Nearly half of the patients with severe outcome had previously visited the ED and were managed as outpatients without antibiotics.

In our study, around a quarter of children with an IBI had previous ED visit before admission, similar to previously published in children with more severe IBIs, such as sepsis and/or meningitis.[3] In that previous study,[3] children with bacterial meningitis or sepsis with repeated ED visits before admission had health outcomes similar to those of children admitted on initial visit. It was argued that both sepsis and meningitis were probably not present at the first visit, not being possible to be diagnosed.[7] This is quite controversial. Recommendations on the management of children with IBIs, and specifically with sepsis, underline the importance of early recognition and considering sepsis in all children with signs or symptoms that indicate possible infection and that delays in the administration of antibiotics worsen outcomes of sepsis and meningitis.[8] In addition, currently, children are brought very promptly to the ED. In a recent study, the median of the duration of the fever in infants younger than 3 months was 2 hours.[9] Such an early consultation may alter the performance of the physical examination to identify patients to be tested for IBI. In our series, no tests were performed on around two-thirds of children not diagnosed on first visit. A sepsis screening tool should be included in a recognition bundle to aid clinicians evaluating children with possible sepsis. For these tools to be effective, all children presenting to the ED should be screened for sepsis and most tools emphasize the use of clinical parameters rather than laboratory tests.[10] However, many febrile children have warning signs of sepsis, but the large majority have nonlife-threatening infections.

The main limitation of our study is that it is a unicenter study, so the conclusions must be cautiously extrapolated to other settings. Although, we consider that results are similar in other pediatric ED of developed countries. This was also a retrospective study being challenging to assess whether clear overall clinical signs were present at the first visit. Nevertheless, all the episodes of our ED are registered electronically making easier to obtain the data in the following month after the visit, although some important items as vital signs were not recorded in all the patients, and it was not possible to analyze them. This reflects a common problem of the pediatric EDs. Finally, sample size limits the ability to do a specific analysis of the sepsis and meningitis. Although, the percentage of children with sepsis and/or meningitis not diagnosed on first visit was similar to that of all IBIs.

Not identifying children with an IBI and not administering antibiotics on the first visit to the ED is associated with a severe outcome. Best practices need to be identified for the early identification and prompt antibiotic administration in children with IBI.

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Late-onset Group B *Streptococcus* Bacteremia Evaluated in the Pediatric Emergency Department and Risk Factors for Severe Infection

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Background: To describe the infants presenting to pediatric emergency departments (PEDs) and diagnosed with group B *Streptococcus* (GBS) late-onset disease (LOD) bacteremia and identify risk factors for severe infection and pediatric intensive care unit (PICU) admission.

Methods: Observational study and subanalysis of a multicenter prospective registry. Setting: pediatric emergency department. Inclusion criteria: infants between 7 and 89 days of age with positive blood culture for GBS seen between 2011 and 2016 at any of 22 Spanish PEDs. Main outcome: risk factors (clinical and laboratory variables) for severe infection (sepsis/septic shock or meningitis) and PICU admission. Second, the prevalence of poor outcomes (acute complications, sequelae or death).

Results: Among 118 patients with LOD, 74 (62.7%) presented a severe infection: 66 sepsis/septic shock (11 with associated meningitis) and 8 meningitis. Thirty-five patients (29.7%) were admitted to a PICU. An altered Pediatric Assessment Triangle (PAT) upon arrival and leukopenia were the only independent risk factors for severe infection [odds ratio (OR): 43.6; 95% confidence interval (CI): 8.1–235.7, $P < 0.01$] and PICU admission (OR: 11.6; 95% CI: 1.5–91.4; $P < 0.019$), respectively. Six patients (5.1%) developed a poor outcome, including 2 deaths (1.7%); all had an altered PAT, elevated procalcitonin (range 4.7–100 ng/ml), and were diagnosed with sepsis/septic shock and admitted to a PICU. Four developed leukopenia.

Conclusions: Infants with GBS LOD frequently develop sepsis/septic shock and bacterial meningitis, associated with non-negligible morbidity and mortality. Clinical appearance was the only risk factor for severe infection, whereas leukopenia was related to PICU admission.

Key Words: bacteremia, children, *Streptococcus agalactiae*, emergency department, sepsis

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INTRODUCTION

Group B *Streptococcus* (GBS) is the second most frequent cause of invasive bacterial infection (IBI) among febrile infants younger than 3 months of age, behind *Escherichia coli*, and it is the leading cause of sepsis and bacterial meningitis in this population.[1–3] GBS infection in these infants is classified into early-onset disease (EOD: neonates 1–6 days old) and late-onset disease (LOD: infants 7–89 days old). The incidence of EOD has declined with the introduction of universal screening of pregnant women for GBS colonization and with the widespread use of intrapartum antibiotic prophylaxis (IAP).[4,5] However, IAP has not been shown to be effective in decreasing LOD;[4,6] in fact, in developed countries where IAP is used for prevention, the relative proportion of EOD and LOD is changing[4] in favor of LOD-GBS disease.

Although GBS is a known cause of bacteremia in febrile infants between the ages of 7 and 89 days, to our knowledge no large series have analyzed GBS infections in pediatric emergency departments (PEDs) for this age group.

The main objective of this study was to describe the epidemiologic and clinical features and laboratory results of infants presenting to participating PEDs and diagnosed with LOD-GBS bacteremia. As a secondary objective, we sought to identify risk factors for severe infection and pediatric intensive care unit (PICU) admission in these patients.

MATERIALS AND METHODS

Database

We performed a secondary analysis of a large, multicenter, cross-sectional prospective registry created in 2010 by the Spanish Society of Pediatric Emergency Medicine and comprising positive blood cultures (BC) obtained in 22 PEDs between 2011 and 2016.

The methodology applied and the BC technique were explained in the parental study.[7] To perform the current secondary analysis, we included infants from the registry between the ages of 7 and 89 days with GBS-related bacteremia.

Data Collection

Data were collected through a standardized online form, which included age, sex, risk factors for EOD GBS, Pediatric Assessment Triangle (PAT) on arrival at the PED, duration and degree of fever, other associated symptoms, physical examination (PE) findings, results of laboratory tests, diagnosis, management and outcome. Medical records were reviewed for all patients, and the parents or caregivers of the infants received a follow-up telephone call within 1 month after the initial visit to the PED to collect further data on the course of the episode.

Definitions

LOD: GBS infection in infants 7–89 days old.

Risk factors for EOD GBS infection included maternal GBS colonization or unknown status and delivery at <37 weeks of gestation.

The PAT was used to assess the overall initial impression of the child. The PAT is a tool used to evaluate appearance, work of breathing, and circulation to skin by using specific and predefined

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physical, visual and auditory findings. If any of these 3 components was abnormal, the patient was considered unstable.

PE was considered to be altered if any findings related to the infectious process were in evidence.

GBS occult bacteremia (OB): isolation of GBS in the blood of a well-appearing febrile infant in the absence of an identifiable focus of infection.

Sepsis: based on the criteria published by Goldstein et al.[8] If a patient presented persistent hypotension and needed vasopressors despite adequate fluid resuscitation, they were diagnosed with septic shock.

Meningitis: isolation of a bacterial pathogen from a cerebrospinal fluid (CSF) culture, detection of a bacterial pathogen in the CSF by molecular methods or isolation of bacteria from BC in a patient with CSF pleocytosis.

Severe LOD-GBS: sepsis/septic shock, meningitis and sepsis/septic shock with associated meningitis.

Poor outcome: acute complications, sequelae or death.

Blood test values considered normal were as follows: white blood cell count (WBC) 5000–15,000/mm^3, absolute neutrophil count (ANC) 1500–10,000/mm^3, C-reactive protein (CRP) <20 mg/L and procalcitonin (PCT) <0.5 ng/ml.

Analysis

Data normality was determined by calculating skewness in relation to standard error values. Normally distributed data were expressed as mean ± standard deviation (SD) and non-normally distributed data as the median and interquartile range (IQR). Two-tailed *t*-tests were used to compare mean values between groups for normally distributed data, and the Mann-Whitney U test was used for non-normally distributed data. Categorical variables are expressed as percentages and were compared using the chi-square test (or Fisher's exact test where expected values were <5 for >25% of cells or <1 for any cell). A *P*-value <0.05 was deemed statistically significant.

The sensitivity of each blood test in identifying GBS bacteremia overall and in distinguishing severe from nonsevere disease was calculated.

Baseline risk factors for severe infection and PICU admission were age, maximum temperature, EOD GBS infection risk factors, altered PAT upon arrival, altered PE upon arrival, WBC (categorized into 3 groups: <5000/mm^3, 5000–15,000/mm^3 and >15,000/mm^3), ANC (categorized into 3 groups: <1500/mm^3, 1500–10,000/mm^3 and >10,000/mm^3); CRP and PCT and were analyzed by means of binary logistic regression. As an exploratory test, backward stepwise regression (likelihood ratio) was performed for those binary variables with a *P*-value <0.2 on univariate analysis. Statistical analyses were performed using STATA v.15.

This study was approved by the Ethics Committee of the Basque Country (approval number PI2011040). Approval for the study and for the sharing of data with the coordinating institution and with the centralized data center was granted by the institutional review board of each participating institution.

RESULTS

Between 2011 and 2016, we recorded 3,936,827 PED episodes and obtained 1696 bacterial isolates in BC [0.04%; 95% confidence interval (CI): 0.04–0.05]. GBS grew in 134 (7.9%, CI: 6.6–9.2) of these cultures, 118 from infants (88.1 %) with LOD (Fig. 1). Table 1 contains the epidemiological and clinical data of these 118 infants.

Seventeen (14.4%) patients with LOD had at least one EOD GBS risk factor: 10 infants with maternal GBS colonization or unknown colonization status, 5 preterm infants and 2 infants with

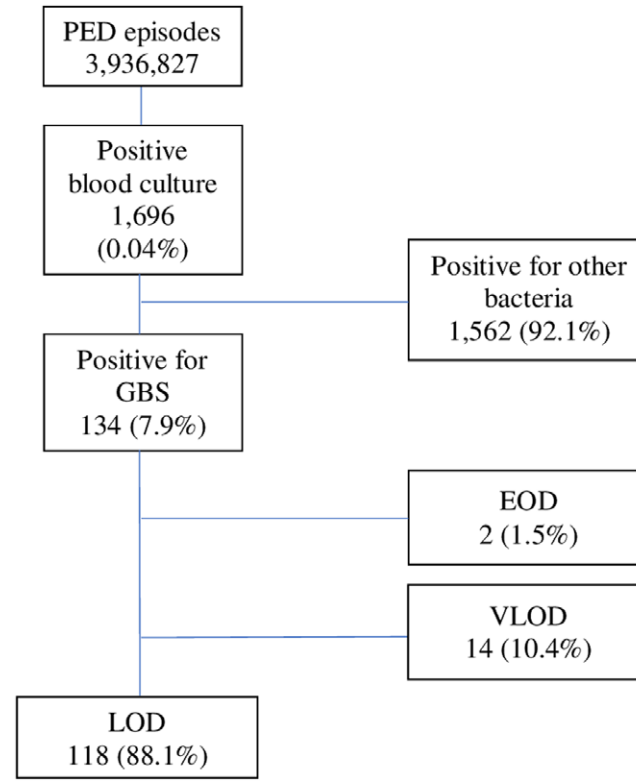

FIGURE 1. Flow-chart indicating included and excluded patients. EOD, early-onset disease; GBS, group B *Streptococcus*; LOD, late-onset disease; PED, pediatric emergency department; VLOD, very late-onset disease. full color online

Table 1. Epidemiologic and clinical features, management, and outcomes of infants with late-onset disease Group B *Streptococcus*

	Late-onset disease (N = 118)
Sex (males), n (%)	68 (57.6)
Age–days, median (IQR)	28 (16–43)
Normal PAT upon arrival, n (%)	56 (47.5)
Reported symptoms, n (%)	
Fever	86 (72.9)
Fever without a source	29 (24,6)
Fever with other symptoms	57 (48.3)
Irritability	38 (32.2)
Somnolence, lethargy	20 (16.9)
Respiratory symptoms	13 (11.0)
Others*	16 (13.6)
Fever, timesince onset–hours, median,(IQR)	2 (0-4)
Normal PE, n (%)	56 (47.5)
Discharge to home, n (%)	3 (2.5)
Admission, n (%)	
Ward	80 (67.8)
PICU	35 (29.7)
Outcomes, n (%)	
Acute complications	6 (5.1)
Sequelae	2 (1.7)
Death	2 (1.7)

*Digestive, local pain.

CI indicates confidence interval; IQR, interquartile range; PAT, Pediatric Assessment Triangle; PE, physical examination; PICU, pediatric intensive care unit.

both risk factors. Two preterm infants with unknown maternal GBS status did not receive IAP; both were diagnosed with sepsis and required PICU admission.

Regarding laboratory findings, WBC and ANC were performed in all patients, CRP was measured in 117 (99.2%) and PCT in 93 (78.8%). Overall, 91 (77.1%) had at least one altered test. The sensitivity of each test was as follows: PCT 80.6% (95% CI: 71.1–88.1), WBC 44.1% (95% CI: 34.9–53.5), ANC 34.7% (95% CI: 26.2–44.1) and CRP 27.4% (95% CI: 19.5–36.4). The sensitivity of the blood tests for diagnosing severe infections is shown in Table 2.

The final diagnosis was sepsis/septic shock in 66 patients (55.9%, 11 with associated meningitis), OB in 40 (33.9%), meningitis in 8 (6.8%) and focal infection in 4 infants [3.4%, 2 osteoarticular and 2 urinary tract infection (UTI)]. Overall, 74 (62.7%) had a severe infection.

Among the patients with severe infection, 15 (20.3%) had normal PAT upon arrival: 7 were neonates younger than 21 days of age and 7 had abnormal values on blood tests. The remaining patient was a 26-day-old neonate diagnosed with cellulitis-adenitis and associated meningitis with normal values on blood tests and no findings of note on arrival to the PED.

From the multivariate model, the baseline risk factors associated with severe infection are shown in Table 3.

GBS was isolated in another location in 20 patients (16.9%): in CSF in 17 patients and in urine in 3 patients. Seven patients had a concomitant UTI caused by another bacterium and one patient had concomitant bacterial meningitis due to *E. coli*.

Admission was required in 115 patients, that is, 80 (67.8%) to the ward and 35 (29.7%) to the PICU. Three patients (2.5%) were discharged home (Table 1): a 35-day-old infant, another 39-day-old patient and another who was 52 days old; all had a normal PAT, normal blood values and were diagnosed with OB. None of the 3 developed a poor outcome.

Table 4 shows the baseline risk factors associated with PICU admission from the multivariate model.

Six (5.1%) patients presented a poor outcome, all of whom were neonates (range 9–26 days of life) with altered PAT, elevated PCT (range 4.7–100 ng/ml), diagnosed with sepsis/septic shock (2 with associated meningitis) and admitted to the PICU. Four had leukopenia (range 2300–9200 WBC/mm^3). All of them presented acute complications: seizures (2), cerebral candidiasis (1), disseminated intravascular coagulopathy (1), endocarditis (1) and pneumonia with pleural effusion (1). Two (1.7%) developed sequelae: one presented a pulmonary valve residual wart and another developed central diabetes insipidus and epileptic encephalopathy. Two patients died (1.7%), including a 12-day-old neonate whose mother was colonized by GBS and received IAP, and another, a 26-day-old infant with a premature (35 weeks) birth with an unknown state of mother's vaginal swab in whom IAP was not administered.

DISCUSSION

Almost two-thirds of the infants with GBS LOD bacteremia studied here presented a severe infection, and around 5% developed acute complications or sequelae, including a mortality rate of nearly 2%. Presenting an altered PAT on arrival to the PED was the only risk factor identified for a severe infection, and this factor also seems to be related to a poor outcome.

Our registry study is one of the largest prospective series analyzing GBS bloodstream infections in infants between the ages of 7 and 89 days. Preliminary data from the original study demonstrated that GBS was the second most common cause of bacteremia among febrile infants younger than 3 months behind *E. coli,*[7] as found in recent multicenter studies.[4,9,10] Compared with data published on *E. coli* bacteremia[11], GBS bloodstream infections are more severe and more frequently lead to sepsis/septic shock and meningitis.[12] Acute complications and deaths are also more frequent with GBS.

In our study, risk factors for EOD GBS infection were present in less than 20% of the infants with GBS LOD. Most of the infants 7–89 days old with a GBS bacteremia were previously healthy and presented no risk factors, thus contrasting with data from studies on EOD[4]. Our results support previous studies finding that IAP does not prevent GBS LOD[4,13] and that other strategies, such as the administration of multivalent vaccines in pregnant women should be considered.[14–16]

PAT alterations are the only independent risk factor for severe infection. An altered PAT should always be considered a risk factor for a poor outcome in pediatric patients. Even so, in our study, only one infant diagnosed with a severe GBS LOD

Table 2. Epidemiologic features, clinical characteristics, laboratory test results, and management with severe and nonsevere infections

	Nonsevere infection* (n = 44)	Severe infection† (n = 74)	*P*-value
Sex (males), n (%, 95% CI)	28 (63.6, 47.8–77.6)	40 (54.1, 42.1–65.7)	n.s.
Risk factors for GBS, n (%, 95% CI)	3 (6.8, 1.4–18.7)	14 (18.9, 10.7–29.7)	n.s.
Age – median days (IQR)	28.5 (16–42.5)	28 (15–43)	n.s.
Normal PAT upon arrival, n (%, 95% CI)	41 (93.2, 81.3–98.6)	15 (20.3, 11.8–31.2)	**<0.001**
Normal PE upon arrival, n (%, 95% CI)	31 (70.5, 54.8–83.2)	25 (33.8, 23.2–45.7)	**<0.001**
Admission			**<0.001**
Ward	37 (84.1, 69.9–93.4)	43 (58.1, 46.1–69.5)	
PICU	4 (9.1, 2.5–21.7)	31 (41.9, 30.5–53.9)	
WBC (median/mm^3, IQR)	11,840 (8300–16,455)	7,300 (4100–11,200)	**<0.001**
Sensitivity (WBC <5000 or >15,000/mcL)	38.6% (95% CI:24.4–54.5%)	35.1% (95% CI: 24.4–47.1%)	
ANC (median/mm^3,IQR)	6,310 (4500–10,598)	4,530 (1975–8,300)	**0.01**
Sensitivity (ANC <1500 or >10,000/mcL)	34.1% (95% CI: 20.5–49.9%)	35.1% (95% CI: 24.2–47.1%)	
CRP (median mg/L, IQR)	5.5 (2.1–18.0)	7.7 (3.6–24.0)	n.s.
Sensitivity (CRP ≥20 mg/L)	23.3% (95% CI: 11.8–38.6%)	29.7% (95% CI: 19.7–41.5%)	
PCT (median ng/ml, IQR)	1.7 (0.4–6.5)	3.5 (0.7–21.8)	n.s.
Sensitivity (PCT ≥0.5 ng/ml)	71.8% (95% CI: 55.1–85.0%)	87.0% (95% CI: 75.1–94.6%)	

*Included: occult bacteremia and focal infection (osteoarticular and urinary tract infection).

†Included: sepsis/septic shock, meningitis, and sepsis/septic shock with associated meningitis.

ANC indicates absolute neutrophil count; CI, confidence interval; CRP, C-reactive protein; GBS, Group B *Streptococcus*; n.s., not significant; PAT, Pediatric Assessment Triangle; PCT, procalcitonin; PE, physical examination; PICU, pediatric intensive care unit; WBC, white blood cell count.

Table 3. Multivariate analysis to identify independent risk factors for severe infection

Risk factors for severe infection	OR	95% CI	*P*-value
Age (days)	0.9	0.95–1.02	n.s.
Maximum temperature (ºC)	0.7	0.4–1.2	n.s.
Altered PAT upon arrival (%)	43.6	8.1–235.7	**<0.001**
Altered PE upon arrival (%)	1.5	0.3–6.9	n.s.
WBC (/mm^3)			
Group 1: <5000	1.5	0.05–45.3	n.s.
Group 2: 5000–15,000	Reference	Reference	
Group 3: >15,000	5.1	0.6–45.4	n.s.
ANC (/mm^3)			
Group 1: <1500	1.2	0.02–86.1	n.s.
Group 2: 1500–10,000	Reference	Reference	
Group 3: >10,000	0.2	0.02–2.3	n.s.
CRP (mg/L)	1.0	0.9–1.0	n.s.
PCT (ng/ml)	1.0	0.9–1.1	n.s.

ANC indicates absolute neutrophil count; CI confidence interval; CRP, C-reactive protein; n.s., not significant; OR, odds ratio; PAT, Pediatric Assessment Triangle; PCT, procalcitonin; PE, physical examination; WBC, white blood cell count.

Table 4. Multivariate analysis to identify independent risk factors for pediatric intensive care unit admission

Risk factors for PICU admission	OR	95% CI	*P*-value
Age (days)	0.9	0.9–1.0	n.s.
Maximum temperature (ºC)	1.0	0.3–3.9	n.s.
GBS infection risk factors (%)	1.4	0.3–6.7	n.s.
Altered PAT upon arrival (%)	7.1	0.9-56-5	n.s.
Altered PE upon arrival (%)	3.2	0.5–21.3	n.s.
WBC (/mm^3)			
Group 1: <5000	11.6	1.5–91.4	**0.019**
Group 2: 5000–15,000	Reference	Reference	
Group 3: >15,000	0.08	0.01–2.2	n.s.
ANC (/mm^3)			
Group 1: <1500	0.8	0.1–8.1	n.s.
Group 2: 1500–10,000	Reference	Reference	
Group 3: >10,000	7.0	0.3–156.7	n.s.
CRP (mg/L)	1.1	0.999–1.14	n.s.
PCT (ng/ml)	1.0	0.968–1.04	n.s.

ANC indicates absolute neutrophil count; CRP, C-reactive protein; CI, confidence interval; GBS, Group B *Streptococcus*; n.s., not significant; OR, odds ratio; PAT, Pediatric Assessment Triangle; PCT, procalcitonin; PE, physical examination; PICU, pediatric intensive care unit; WBC, white blood cell count.

had a normal PAT upon arrival to the PED, including 7 of the 10 patients with meningitis. This could be partially explained by the short history of symptoms at the time of PED assessment and by the young age of these infants, which makes it more difficult to properly implement the PAT. In fact, most infants in our sample were brought to the PED after only a few hours of fever (median 2 hours), and 11 of the 15 infants with a severe infection and normal PAT were neonates.

Clinical decisions regarding these infants should be supported by laboratory tests (blood, urine and CSF) in addition to PAT and PE to identify infants at high risk of IBI, as recommended by a majority of the validated approaches for febrile infants ≤90 days old.[17,18] PCT was the blood biomarker with the highest sensitivity (80.6% vs. 27.4% for CRP); indeed, PCT sensitivity was even higher for identifying a severe infection, while CRP sensitivity remained poor.[19,20] The short time between the symptom onset and presentation to the PED could explain this finding, since CRP is generally not detectable in serum until 12 hours after the onset of inflammation,[21] whereas PCT has a faster kinetic. With the exception of one 26-day-old neonate, all infants in our series with severe infections and normal PAT fulfilled the high-risk criteria for IBI, such as age under 21 days or abnormal analytical values,[18] and antibiotic therapy was administered in all cases. The aforementioned neonate did not develop a poor outcome.

Leukopenia was the only independent risk factor for PICU admission. Curiously, leukopenia in well-appearing infants was not found to be a risk factor for a poor outcome, thus contrasting with previous reports.[22,23]

On the one hand, a significant number of GBS colonizations were isolated in locations other than the blood (20, 16.9%), mainly CSF (17, 14.4%). This reaffirms the current recommendation to perform a lumbar puncture, if it has not been done before, when GBS bacteremia is identified in infants under 3 months of age.[24] GBS was also isolated concomitantly in urine, but much less frequently (2.5%), as reported in previous studies.[9] On the other hand, 8 (6.8%) other infants had a positive culture for other microorganisms, 7 in urine (3 UTI) and 1 CSF culture. All were Gram-negative microorganisms, which are the most common in these infants.[9]

Our study has certain limitations. First, it was not specifically designed to investigate GBS in patients with positive bloodstream culture. Not all known GBS risk factors have been considered in our registry, as only maternal GBS colonization or unknown status and delivery at <37 weeks of gestation have been reported. Second, although the same criteria were established to detect sepsis/septic shock, some infants may have been misclassified. Third, PICU admission did not follow the same criteria and may have varied from one hospital to another. Additionally, the indication for respiratory and hemodynamic support was also unknown. Nevertheless, we believe that the data collected allow us to characterize GBS LOD and may help to better identify these children in the PED, especially those with severe infection.

We conclude that infants with LOD due to GBS frequently develop sepsis/septic shock and bacterial meningitis with nonnegligible morbimortality, especially those infants with an altered PAT and leukopenia. Different prevention strategies are necessary for these infants.

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Ana Blázquez), Hospital Universitario Infanta Sofía (Alfredo Tagarro, Esteban Aznar), Hospital Universitari Sant Joan de Reus (Neus Rius, Clara Calbet), Hospital General de Catalunya (Esther Oliva), Hospital Universitario Reina Sofía (Francisca Aguilar, Angela Bello), Hospital Universitario Río Hortega (María Nathalie Campo Fernández, Garazi Fraile), Hospital del Tajo (Clara García-Bermejo), S.A.M.U.R. - Municipal Emergency and Rescue Assistance Service (Nieves de Lucas).

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    - Quartil: Q3

Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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CARTAS CIENTÍFICAS

Impacto de la pandemia de COVID-19 en las infecciones bacterianas invasivas en urgencias☆

Impact of the COVID-19 pandemic on pediatric invasive bacterial infections

Sra. Editora,

Durante la pandemia por el SARS-CoV-2 hubo una disminución de las consultas en los servicios de urgencias de pediatría (SUP) a nivel internacional[1]. Las medidas de protección adoptadas se acompañaron de una disminución de la incidencia de las infecciones bacterianas invasivas (IBI) transmitidas por vía respiratoria, como las causadas por *S. pneumoniae*, *N. meningitidis* y *H. influenzae*[2,3]. Otras IBI (por *E. coli* y *S. agalactiae*), más propias de niños más pequeños, no mostraron ese descenso[3]. Para nuestro conocimiento, estas variaciones no han sido analizadas en nuestro entorno ni tampoco se ha analizado si durante la pandemia varió la probabilidad de que un niño atendido en un SUP fuera diagnosticado de una IBI.

El objetivo principal de este estudio es analizar el impacto de la pandemia por el SARS-CoV-2 en la epidemiología de las IBI en SUP y en la probabilidad de que un niño menor de 14 años previamente sano que acude al SUP sea diagnosticado de una IBI.

En nuestro SUP existe un registro que incluye todas las IBI diagnosticadas desde 2008 ya explicado en previas publicaciones[4]. Se definió IBI como la identificación de una bacteria patógena en sangre o líquido cefalorraquídeo, excluyéndose los pacientes en los que se aisló una bacteria en el hemocultivo, clásicamente considerada como contaminante. Para este estudio, se analizó a los pacientes menores de 14 años previamente sanos diagnosticados de IBI en el SUP entre 2017 y 2022. Se compararon las características e incidencia de IBI en 2 periodos: prepandemia (2017-2019) y pandemia (marzo de 2020-diciembre de 2022). El periodo de pandemia se dividió en función de las medidas de protección adoptadas (higiénicas y de distancia social) y la afluencia a los SUP: 2020 (medidas más estrictas y menor afluencia al SUP) y 2021 y 2022 (medidas menos estrictas y mayor afluencia a los SUP). El estudio fue aprobado por el Comité de Ética e Investigación del hospital (código E22/36).

Durante el periodo de estudio se registraron en el SUP 269.105 episodios (153.736 prepandemia, con 4.270 episodios/mes, y 115.369 en pandemia, con 3.393 episodios/mes; $\Delta = -20{,}5\%$) y 119 pacientes menores de 14 años previamente sanos (0,04%) fueron diagnosticados de IBI. En el periodo prepandemia se diagnosticaron 70 IBI y se diagnosticaron 49 en la pandemia. Durante esta última, la probabilidad de diagnosticar de IBI a un paciente previamente sano varió de forma significativa: fue superior en 2020. En 2021, con medidas menos estrictas y mayor afluencia a los SUP, el número de IBI/mes fue inferior al de prepandemia, al igual que la probabilidad de diagnosticar de IBI a un paciente previamente sano. En 2022, de manera global, la situación fue similar a la prepandemia (tabla 1).

Durante la pandemia varió de manera notable la probabilidad de que un paciente previamente sano que consultaba en urgencias presentara una IBI. Cuando las medidas de protección fueron más estrictas y fue menor la afluencia a los SUP, la tasa de IBI/mes se mantuvo estable respecto a años previos. Sin embargo, esto comportó que la probabilidad de que un paciente previamente sano fuera diagnosticado de una IBI se incrementara de forma significativa, disminuyendo de nuevo cuando las medidas se relajaron y la afluencia a los SUP fue mayor. La disminución de la probabilidad de ser diagnosticado de una IBI cuando las medidas se relajaron era esperable por el aumento que se produce en la transmisión de infecciones virales, que pasan a ser mucho más frecuentes. Sin embargo, no encontramos explicación para esa disminución del número absoluto de pacientes diagnosticados de una IBI en el segundo año de la pandemia. Consideramos relevante que esta información sea conocida por los médicos que atienden a estos pacientes, ya que se podría pensar, incorrectamente, que, dado que existe una menor transmisibilidad de IBI por vía respiratoria, la probabilidad de que un niño que acude a Urgencias sea diagnosticado de IBI es menor. Además, la variación de la prevalencia de IBI podría también afectar al rendimiento de diferentes reglas de predicción clínica o de los sistemas utilizados para la identificación de pacientes con IBI. La no detección de bacterias transmisibles por vía respiratoria cuando las medidas de protección eran más estrictas, como la *N. meningitidis*, ya había sido reportada[2,3]. Por último, en el año 2022 se objetiva un importante repunte de las infecciones invasivas neumocócicas, que llegaron a ser el 40,9% de las IBI diagnosticadas.

A pesar de las limitaciones de nuestro estudio, derivadas de ser unicéntrico y de su pequeño tamaño muestral, pensamos que estos hallazgos refuerzan la necesidad de diseñar sistemas de vigilancia robustos que monitoricen la evolución de las IBI con el fin de poder utilizar estos datos para

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Tabla 1 Episodios totales e infecciones bacterianas invasivas (IBI) registradas en el servicio de urgencias pediátrico (SUP) antes y durante la pandemia por SARS-CoV-2

	Episodios en SUP	Episodios/mes	IBI	IBI/mes	IBI/episodios	Bacterias más prevalentes (%)
Prepandemia	153.736	4.270	70	1,94	1 IBI / 2.196	*S. pneumoniae* (18,6) *N. meningitidis* (18,6) *S. aureus* (17,1) *E. coli* (15,7) *S. agalactiae* (5,7)
Pandemia						
2020	21.746	2.175	19	1,90	1 IBI / 1.144*	*S. pneumoniae* (28,6) *S. aureus* (20,4) *N. meningitidis* (10)
2021	39.880	3.323	8	0,67*	1 IBI / 4.985*	*S. agalactiae* (10)
2022	53.743	4.478	22	1,83	1 IBI / 2.443	*E. coli* (10)

En el periodo de pandemia, los cambios destacables respecto a las bacterias responsables fueron la desaparición de *N. meningitidis* durante el 2021 y el aumento de *S. pneumoniae* en 2022 (9/22; 40,9% de las IBI diagnosticadas).
En menores de 3 meses, el *S. agalactiae* fue el principal causante de las IBI en la pandemia (33,3%) vs. *E. coli* (50%) en prepandemia.
* $p < 0,01$, al comparar con el periodo prepandemia.

que tanto el sistema sanitario como los profesionales estén preparados en caso de presentarse de nuevo una situación similar a la vivida durante la pandemia.

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Validez de las ecuaciones CEEW para la estimación de peso en pacientes pediátricos españoles

Validity of CEEW equations for weight estimation in Spanish pediatric patients

Sra. Editora:

En ninguna otra población de pacientes hay más cálculo y manipulación de las dosis de medicamentos que en la edad pediátrica, por lo que la atención de emergencias pediátricas supone un verdadero reto para el personal sanitario. El conocimiento del peso exacto del niño es importante porque de este valor va a depender el cálculo de las dosis de medicamentos, pero no siempre es una información fácilmente disponible.

Para solventar este problema, tradicionalmente se han utilizado variedad de métodos de estimación de peso basados en variables indirectas, pero prácticamente todas presentan limitaciones de validez relacionadas con la diversidad étnica, biológica y sociodemográfica[1,2].

Una de las últimas estrategias de estimación de peso que se han publicado son las fórmulas Children's European Estimator of Weight (CEEW). La fórmula CEEW1 estima peso a

HELBURU BAKOITZAREKIN HARREMANDUTAKO ARTIKULUAK

1. Hamalau urtetik beherako pazienteetan baieztatu diren IBIen aurkezpen klinikoaren karakterizazioa egin.
    - Characteristics of children with microbiologically confirmed invasive bacterial infections in the emergency department. EJEM 2018.
    - Repeated Emergency Department Visits Among Children with Invasive Bacterial Infections. PIDJ 2021.
2. Hamalau urtetik beherako pazienteen IBIen larritasuna deskribatu.
    - Characteristics of children with microbiologically confirmed invasive bacterial infections in the emergency department. EJEM 2018.
    - Repeated Emergency Department Visits Among Children with Invasive Bacterial Infections. PIDJ 2021.
3. Hamalau urtetik beherako pazienteen IBIak identifikatzeko egiten diren ohiko odol testen (leukozitoen zenbaketa, neutrofiloen zenbaki absolutua, proteina C erreaktiboa eta prokaltzitonina) balioa analizatu.
    - Markers for invasive bacterial infections in previously healthy children. Am J Emerg Med. 2021.
4. Fokurik gabeko sukarra duten eta larrialdi zerbitzura egonkor iristen diren 3-24 hilabete arteko haurrak artatzerakoan odol testik ez erabiltzearen gomendioa ebaluatu.
    - Prevalence of Occult Bacteremia in Infants With Very High Fever Without a Source. PIDJ 2018.

- Occult Bacteremia in Young Children with Very High Fever Without a Source: A Multicenter Study. PIDJ 2020.

5. *E. coli*k eragindako infekzio inbaditzaileen aurkezpena deskribatu eta balizko profilak eta larritasunarekiko balizko harremana ikertu.
    - Paediatric *Escherichia coli* bacteraemia presentations and high-risk factors in the emergency department. Acta Paediatr 2021.
6. B taldeko estreptokokoak eragindako infekzio inbaditzailearen aurkezpena deskribatu eta haren larritasunarekiko balizko harremana ikertu.
    - Late-onset Group B *Streptococcus* Bacteremia Evaluated in the Pediatric Emergency Department and Risk Factors for Severe Infection. PIDJ 2022.
7. Bigarren mailako helburua. Aurretik espero ez genuen pandemia batek larrialdi zerbitzu baten identifikatu diren IBIen epidemiologian izan duen eragina deskribatu.
    - Impact of the COVID-19 pandemic on pediatric invasive bacterial infections. An Pediatr (Engl Ed) 2023.

Tesiarekin harreman zuzenik izan ez arren larrialdi zerbitzu pediatrikoan gaixotasun infekziosoen inguruan egindako ikerketen argitalpenak puntu honetan gehituko ditugu.

- van Houten CB, Naaktgeboren CA, Ashkenazi-Hoffnung L, Ashkenazi S, Avis W, Gangoiti I, Bont LJ et al; IMPRIND consortium. Expert panel diagnosis demonstrated high reproducibility as reference standard in infectious diseases. J Clin Epidemiol. 2019 Aug;112:20-27. doi: 10.1016/j.jclinepi.2019.03.010. Epub 2019 Mar 28. PMID: 30930247.
    - ISSN: 0895-4356

- JCR: Science edition, 2019
- Impact factor: 2,702
- Quartil: Q1
- Abstract:

Objective: If a gold standard is lacking in a diagnostic test accuracy study, expert diagnosis is frequently used as reference standard. However, interobserver and intraobserver agreements are imperfect. The aim of this study was to quantify the reproducibility of a panel diagnosis for pediatric infectious diseases.

Study design and setting: Pediatricians from six countries adjudicated a diagnosis (i.e., bacterial infection, viral infection, or indeterminate) for febrile children. Diagnosis was reached when the majority of panel members came to the same diagnosis, leaving others inconclusive. We evaluated intraobserver and intrapanel agreement with 6 weeks and 3 years' time intervals. We calculated the proportion of inconclusive diagnosis for a three-, five-, and seven-expert panel.

Results: For both time intervals (i.e., 6 weeks and 3 years), intrapanel agreement was higher (kappa 0.88, 95%CI: 0.81-0.94 and 0.80, 95%CI: NA) compared to intraobserver agreement (kappa 0.77, 95%CI: 0.71-0.83 and 0.65, 95%CI: 0.52-0.78). After expanding the three-expert panel to five or seven experts, the proportion of inconclusive diagnoses (11%) remained the same.

Conclusion: A panel consisting of three experts provides more reproducible diagnoses than an individual expert in children with lower respiratory tract infection or fever without source. Increasing the size of a

panel beyond three experts has no major advantage for diagnosis reproducibility.

Keywords: Diagnosis; Expert panel; Gold standard; Infectious diseases; Reference standard; Reproducibility.

- Gangoiti I, Martinez-Fernandez E, Garmendia O, Diez A, Mintegi S. Impacto de la vacunación en embarazadas sobre la reemergencia de la tosferina y su forma de presentación en urgencias [Impact of whooping cough vaccine during pregnancy on the resurgence of the disease and its form of presentation in paediatric emergency departments]. An Pediatr (Engl Ed). 2020 Aug;93(2):129-131. Spanish. doi: 10.1016/j.anpedi.2019.11.002. Epub 2019 Dec 27. PMID: 31889662.
    - ISSN: 2341-2879
    - JCR: Science edition, 2020
    - Impact factor: 1,5
    - Quartil: Q3
    - Abstract:

      Introduction: The resurgence of pertussis led to immunize pregnant women in 2015. The objective is to analyse the impact of immunizing pregnant women on the resurgence and way of presentation of pertussis in a paediatric emergency department (ED).

      Methods: Retrospective cohort analysis between 2008 and 2017. We compared the episodes with a diagnosis of pertussis before and after immunizing pregnant women.

Results: During the study period, 196 children were diagnosed with pertussis. In the pre-vaccine period, we diagnosed initially 1 episode of pertussis/8903 episodes in the ED vs 1/1178 in 2015, decreasing to 1/3203 episodes after vaccination. The median age of patients diagnosed with pertussis increased after vaccination (9 vs. 38 months, p = 0,02) and the admission rate dropped from 36.9% to 8.8% (p < 0.01).

Conclusion: Vaccination has reversed the trend of rising pertussis cases in the paediatric ED, decreasing the number of more severe episodes.

- Funk AL, Florin TA, Kuppermann N, Tancredi DJ, Xie J, Gangoiti I, Freedman SB et al; Pediatric Emergency Research Network-COVID-19 Study Team. Outcomes of SARS-CoV-2-Positive Youths Tested in Emergency Departments: The Global PERN-COVID-19 Study. JAMA Netw Open. 2022 Jan 4;5(1):e2142322. doi: 10.1001/jamanetworkopen.2021.42322. PMID: 35015063; PMCID: PMC8753506.
    - ISSN: 2574-3805
    - JCR: Science edition, 2022
    - Impact factor: 4,108
    - Quartil: Q1
    - Abstract:

      Importance: Severe outcomes among youths with SARS-CoV-2 infections are poorly characterized.

Objective: To estimate the proportion of children with severe outcomes within 14 days of testing positive for SARS-CoV-2 in an emergency department (ED).

Design, setting, and participants: This prospective cohort study with 14-day follow-up enrolled participants between March 2020 and June 2021. Participants were youths aged younger than 18 years who were tested for SARS-CoV-2 infection at one of 41 Eds across 10 countries including Argentina, Australia, Canada, Costa Rica, Italy, New Zealand, Paraguay, Singapore, Spain, and the United States. Statistical analysis was performed from September to October 2021.

Exposures: Acute SARS-CoV-2 infection was determined by nucleic acid (eg, polymerase chain reaction) testing.

Main outcomes and measures: Severe outcomes, a composite measure defined as intensive interventions during hospitalization (eg, inotropic support, positive pressure ventilation), diagnoses indicating severe organ impairment, or death.

Results: Among 3222 enrolled youths who tested positive for SARS-CoV-2 infection, 3221 (>99.9%) had index visit outcome data available, 2007 (62.3%) were from the United States, 1694 (52.6%) were male, and 484 (15.0%) had a self-reported chronic illness; the median (IQR) age was 3 (0-10) years. After 14 days of follow-up, 735 children (22.8% [95% CI, 21.4%-24.3%]) were hospitalized, 107 (3.3% [95% CI, 2.7%-4.0%]) had severe outcomes, and 4 children (0.12% [95% CI, 0.03%-0.32%]) died. Characteristics associated with severe outcomes included being aged 5 to 18 years (age 5 to <10 years vs <1 year: odds ratio [OR], 1.60 [95% CI,

1.09-2.34]; age 10 to <18 years vs <1 year: OR, 2.39 [95% CI 1.38-4.14]), having a self-reported chronic illness (OR, 2.34 [95% CI, 1.59-3.44]), prior episode of pneumonia (OR, 3.15 [95% CI, 1.83-5.42]), symptoms starting 4 to 7 days prior to seeking ED care (vs starting 0-3 days before seeking care: OR, 2.22 [95% CI, 1.29-3.82]), and country (eg, Canada vs US: OR, 0.11 [95% CI, 0.05-0.23]; Costa Rica vs US: OR, 1.76 [95% CI, 1.05-2.96]; Spain vs US: OR, 0.51 [95% CI, 0.27-0.98]). Among a subgroup of 2510 participants discharged home from the ED after initial testing and who had complete follow-up, 50 (2.0%; 95% CI, 1.5%-2.6%) were eventually hospitalized and 12 (0.5%; 95% CI, 0.3%-0.8%) had severe outcomes. Compared with hospitalized SARS-CoV-2-negative youths, the risk of severe outcomes was higher among hospitalized SARS-CoV-2-positive youths (risk difference, 3.9%; 95% CI, 1.1%-6.9%).

Conclusions and relevance: In this study, approximately 3% of SARS-CoV-2-positive youths tested in Eds experienced severe outcomes within 2 weeks of their ED visit. Among children discharged home from the ED, the risk was much lower. Risk factors such as age, underlying chronic illness, and symptom duration may be useful to consider when making clinical care decisions.

- Funk AL, Kuppermann N, Florin TA, Tancredi DJ, Xie J, Gangoiti I, Freedman SB et al; Pediatric Emergency Research Network–COVID-19 Study Team. Post-COVID-19 Conditions Among Children 90 Days After SARS-CoV-2 Infection. JAMA Netw Open. 2022 Jul 1;5(7):e2223253. Doi:

10.1001/jamanetworkopen.2022.23253. Erratum in: JAMA Netw Open. 2022 Aug 1;5(8):e2231131. PMID: 35867061; PMCID: PMC9308058.

- ISSN: 2574-3805
- JCR: Science edition, 2022
- Impact factor: 4,108
- Quartil: Q1
- Abstract:

  Importance: Little is known about the risk factors for, and the risk of, developing post-COVID-19 conditions (PCCs) among children.

  Objectives: To estimate the proportion of SARS-CoV-2-positive children with PCCs 90 days after a positive test result, to compare this proportion with SARS-CoV-2-negative children, and to assess factors associated with PCCs.

  Design, setting, and participants: This prospective cohort study, conducted in 36 emergency departments (EDs) in 8 countries between March 7, 2020, and January 20, 2021, included 1884 SARS-CoV-2-positive children who completed 90-day follow-up; 1686 of these children were frequency matched by hospitalization status, country, and recruitment date with 1701 SARS-CoV-2-negative controls.

  Exposure: SARS-CoV-2 detected via nucleic acid testing.

  Main outcomes and measures: Post-COVID-19 conditions, defined as any persistent, new, or recurrent health problems reported in the 90-day follow-up survey.

  Results: Of 8642 enrolled children, 2368 (27.4%) were SARS-CoV-2 positive, among whom 2365 (99.9%) had index ED visit disposition data

available; among the 1884 children (79.7%) who completed follow-up, the median age was 3 years (IQR, 0-10 years) and 994 (52.8%) were boys. A total of 110 SARS-CoV-2-positive children (5.8%; 95% CI, 4.8%-7.0%) reported PCCs, including 44 of 447 children (9.8%; 95% CI, 7.4%-13.0%) hospitalized during the acute illness and 66 of 1437 children (4.6%; 95% CI, 3.6%-5.8%) not hospitalized during the acute illness (difference, 5.3%; 95% CI, 2.5%-8.5%). Among SARS-CoV-2-positive children, the most common symptom was fatigue or weakness (21 [1.1%]). Characteristics associated with reporting at least 1 PCC at 90 days included being hospitalized 48 hours or more compared with no hospitalization (adjusted odds ratio [aOR], 2.67 [95% CI, 1.63-4.38]); having 4 or more symptoms reported at the index ED visit compared with 1 to 3 symptoms (4-6 symptoms: aOR, 2.35 [95% CI, 1.28-4.31]; ≥7 symptoms: aOR, 4.59 [95% CI, 2.50-8.44]); and being 14 years of age or older compared with younger than 1 year (aOR, 2.67 [95% CI, 1.43-4.99]). SARS-CoV-2-positive children were more likely to report PCCs at 90 days compared with those who tested negative, both among those who were not hospitalized (55 of 1295 [4.2%; 95% CI, 3.2%-5.5%] vs 35 of 1321 [2.7%; 95% CI, 1.9%-3.7%]; difference, 1.6% [95% CI, 0.2%-3.0%]) and those who were hospitalized (40 of 391 [10.2%; 95% CI, 7.4%-13.7%] vs 19 of 380 [5.0%; 95% CI, 3.0%-7.7%]; difference, 5.2% [95% CI, 1.5%-9.1%]). In addition, SARS-CoV-2 positivity was associated with reporting PCCs 90 days after the index ED visit (aOR, 1.63 [95% CI, 1.14-2.35]), specifically systemic health problems (eg, fatigue, weakness, fever; aOR, 2.44 [95% CI, 1.19-5.00]).

Conclusions and relevance: In this cohort study, SARS-CoV-2 infection was associated with reporting PCCs at 90 days in children. Guidance and follow-up are particularly necessary for hospitalized children who have numerous acute symptoms and are older.

ARTIKULUAK GARATZEKO METODOA

Erregistro prospektibo unizentriko baten oinarritutako lanak

- Gangoiti I, Valle JR, Sota M, Martinez-Indart L, Benito J, Mintegi S. Characteristics of children with microbiologically confirmed invasive bacterial infections in the emergency department. Eur J Emerg Med. 2018 Aug;25(4):274-280. doi: 10.1097/MEJ.0000000000000453. PMID: 28118320.
- Gangoiti I, Fernandez CL, Gallego M, Gomez B, Benito J, Mintegi S. Markers for invasive bacterial infections in previously healthy children. Am J Emerg Med. 2021 Oct;48:83-86. doi: 10.1016/j.ajem.2021.04.018. Epub 2021 Apr 13. Erratum in: Am J Emerg Med. 2021 Apr 22;: PMID: 33862390.
- Gangoiti I, Gorostizaga Z, Aranzamendi M, Gomez B, Benito J, Mintegi S. Repeated Emergency Department Visits Among Children with Invasive Bacterial Infections. Pediatr Infect Dis J. 2021 May 1;40(5):e205-e207. doi: 10.1097/INF.0000000000003062. PMID: 33464016
- Martin-Irazabal G, Gangoiti I, Gomez B, Lizarraga L, Mintegi S. Impact of the COVID-19 pandemic on pediatric invasive bacterial infections. An Pediatr (Engl Ed). 2023 Mar;98(3):228-229. doi: 10.1016/j.anpede.2023.01.013. Epub 2023 Feb 20. PMID: 36813615; PMCID: PMC9940794

2008an ireki zen prospektiboki erregistratutako data basean oinarritutako kohorte-ikerketa baten emaitza dira lan hauek. Hirugarren mailako ospitale bateko larrialdi zerbitzu pediatriko batean, 14 urtetik beherako pazienteetan diagnostikatu diren IBIak

bildu ditu. Larrialdi zerbitzu hau, hirugarren mailako irakaskuntza ospitale baten parte da eta urtero, 14 urtez azpiko 55.000 pazienteren bueltan artatzen ditu.

Larrialdi zerbitzu pediatrikoan IBI bat diagnostikatzen zaion paziente bakoitza, ospitaleak bereak dituen erregistro elektronikoen bitartez identifikatzen da. Hilero, mikrobiologia zerbitzuak gainbegiratzen duen lagin guztien kultiboak biltzen dituen txostena jasotzen du ikertzaile nagusiak. Honek odol eta LZR laginetan hazi diren mikroorganismo patogenoen eta PCR bitartez bereizitako *N. meningitidis* eta *S. pneumoniae*ren identifikazioa baieztatzen du eta horiei loturiko Osasun Publikoko Sistemaren Larrialdi Zerbitzu Pediatrikoetako gertakari txostena berraztertu.

Erregistroan ondorengo datuak batu ziren:

- Adina
- Sexua
- Aurrekariak
- Kontsulta burutu den urte eta hilabetea
- Neumokokoaren aurkako txertaketa egoera
- Etxean erregistratu den tenperatura maximoa
- Larrialdi zerbitzu pediatrikoan neurtu den tenperatura
- Gertaera berarekin zerikusia duten aurreko eta geroko kontsulta (odol kultura lortu den gertaera eguna delarik abiapuntu)
- Balizko lotutako sintomak
- Larrialdi zerbitzura iristean duen egoera (ebaluazio pediatrikorako triangelua)
- Azterketa fisikoa
- Odol probak (leukozitoen zenbaketa, neutrofiloen zenbaki absolutua, C proteina erreaktiboa, prokaltzitonina)

- Kultura eta PCR bidezko identifikazio probak
- Toraxeko erradiografia
- Gernu eta likido zefalorrakideoan burututako probak, analisi biokimikoa, kultura eta PCR bidezko identifikazio probak
- Beste kultura batzuk
- Isolatu den mikroorganismoa
- Azken diagnostikoa
- Norakoa
- Bilakaera

Definizio garrantzitsuenak tesi honen sarreran aipatzen joan garenak izan dira, artikuluz artikulu errepikatu direnak.

- Infekzio bakteriano inbasiboa (IBI): Odolean eta/edo likido zefalorrakideoan egiten den benetako bakterio patogeno baten identifikazioa bakterio hazkuntza bidez eta/edo *N. meningitidis* eta *S. pneumoniae*ren detekzio genomikoa lortuz PCR teknika erabiliz (gure kasuan, RealCycler MENE eta RealCycler MENELI; Progenie Molecular, Valentzia, Espainia). Klasikoki kutsagarritzat jotzen den bakterio-espezie bat (*Staphylococcus epidermidis*, *Propionibacterium acnes*, *Streptococcus viridans*, *Corynebacterium spp*., beste difteroide batzuk eta bestelakoak barne) isolatu zen odol edo likido zefalorrakideo lagina baztertu egiten zen aurretiaz osasuntsu zen paziente batetik etorriz gero. Kateterrarekin lotutako odol-infekzioaren behin betiko diagnostikoa egiteko, kateter muturren edo kateter/dispositiboetatik ateratako odol-kulturaren emaitza positiboak beharrezkoak ziren.

- Aurrez osasuntsua den pazientea. Infekzio larri bat erraz dezakeen arrisku-faktore hauetakoren bat pairatzen ez duen pazientea: immunogutxiegitasuna (gaixotasun onkologikoa, giltzurrun-gutxiegitasun kronikoa, transplantea jaso duen pazientea, anemia drepanozitikoa sufritzen duen pazientea, immunogutxiegitasuna eragiten duen medikazioa hartzen duen pazientea, jaioberri oso goiztiarra,…); gailu mekaniko baten presentzia (kateter iraunkorra, shunt bentrikuloperitoneala); edota aurreko 10 egunetan prozedura diagnostiko-terapeutiko inbaditzailea jasan duen pazientea.
- Itxura ona duen pazientea: ebaluazio pediatrikorako triangelu egonkorra duen pazienteak (Gausche-Hill M, 2003) larrialdi zerbitzu pediatrikora iristen direnean.
- Bakteriemia ezkutua: Sukarraz gain, inolako zeinu eta sintomarik ez duen pazientearen odolean benetako bakteria baten isolamendua.
- Sepsia: organismoak, balizko infekzio edo/eta baieztatutako infekzio baten aurrean ematen duen hantura-erantzun sindrome sistemikoa da (Goldstein B, 2005).
- Sepsi larria: Goldstein et al.ek adostutako sepsiaren definizoari kriterio hauek gehitu zaizkio: disfuntzio kardiobaskularra, arnas zailtasun sindrome akutua edo/eta bestelako bi sistemen disfuntzioa (Goldstein B, 2005) (Gómez Cortés, 2020).
- Shock septikoa: Shock septikoa, 40ml/kg-rainoko likido isotonikoen administrazioak egonkortzen ez duen sepsi eta disfuntzio organikoa (Goldstein B, 2005).
- Larritasun kriterioak: IBIa pairatu eta haren ondorioz, ondorengo 12 hilabeteko epean gertatu den heriotza edo iraunkorrak diren sekuelen mantenua. Sekuela,

IBIaren ondorioz agertu den morbilitate egoera gisa definituko da. Artikuluren baten zainketa unitateen beharra izatea bera ere larritasun kriterio definitu da.

Definizio espezifikoak:

- Balio analitiko normalak: Orokorrean onartuen dauden balioen arabera, ondokoak kontsideratu ziren balio normal moduan: leukozitoen zenbaketa 5.000 eta 15.000/mm^3 bitartean; neutrofiloen zenbaki absolutua 1.500 eta 10.000/mm^3 bitartean; Proteina C-erreaktiboa 20mg/L-tik behera eta prokaltzitonina 0,5ng/ml-tik behera.
- Fokurik gabeko sukarra: Haren jatorria zein den adieraz dezakeen zeinu edo sintomarik azaltzen ez duen sukarrari deritzo; hala nola, eztula, beherakoa, amigdalen hantura, auskultazio patologikoa, polipnea, zeinu meningeoak,…

Analisi estadistikoari dagokionez SPSS Statistics for Windows programaren 21.0 eta 23.0 bertsioa erabiliz egin zen (IBM, Armonk, New York, AEB). Aldagai kualitatiboak maiztasun eta ehuneko absolutuak erabiliz deskribatu ziren, eta aldagai jarraikiak batez besteko eta desbiazio estandar edo mediana eta kuartil arteko tarteak erabiliz. Aldagai kualitatiboen arteko lotura aztertzeko Chi-karratuaren proba erabili zen. Poissonen erregresio-ereduak erabili ziren denbora-tarte jakinetan IBI pneumokokoaren intzidentzia-tasak aztertzeko. Aldagai anitzeko erregresio logistiko bitarra egin zen prozesuaren larritasun handiagoarekin lotutako arrisku-faktore independenteak identifikatu asmoz. Hasiera baten, aldagai bakarreko erregresio logistikoko analisia egin zen. p balioa 0,2 baino txikiagoa zuten aldagai guztiak aldagai anitzeko eredu ez-automatiko baten sartu ziren; gerora p balioa 0,05 baino txikiagoa zutenak, aldagai anitzeko azken ereduan sartzeko. Ereduaren emaitzak odds ratio eta %95eko konfiantza-

tarte gisa aurkeztu ziren. Espezifikotasun eta etekin diagnostikoaren kurba (ROC kurba) eta kurbaren azpiko azalera ere kalkulatu ziren. Ereduaren egokitzeko gaitasuna Hosmer-Lemeshow probaren bitartez ebaluatu zen.

Pazienteen karakterizazio helburu zuen ikerketan izan ezik, gainontzeko hiruretan, aurretiaz osasuntsu ziren pazienteak baino ez ziren ereduetan sartu. Odol markatzaileak ikertzea zuenaren kasuan, bakoitzaren sentikortasuna kalkulatu zen azken diagnostiko eta mikroorganismo eragilearen arabera. Pandemiaren eragina ikertzea helburu zuenean, aldiz, bi garai ezberdindu ziren euren artean IBIen intzidentzia eta ezaugarriak ikertzeko: pandemia-aurreko garaia (2017-2019) eta garai pandemikoa (2020ko martxotik 2022ko abendura).

Ikerkuntza unizentriko baten oinarritutako artikulua

- Gangoiti I, Rodriguez E, Zubizarreta A, Benito J, Mintegi S. Prevalence of Occult Bacteremia in Infants With Very High Fever Without a Source. Pediatr Infect Dis J. 2018 Nov;37(11):e271-e273. doi: 10.1097/INF.0000000000001955. PMID: 29462106.

Azterketa erretrospektiboa, deskribatzaile eta analitikoa, Osasun Publikoko Sistemaren parte den hirugarren mailako irakaskuntza ospitale baten larrialdi zerbitzu pediatrikoetan burututakoa. Ikertutako populazioa 2013ko urtarriletik 2016eko abendurarte larrialdi zerbitzu pediatrikoan artatutako 3-24 hilabete bitarteko haurrak izan ziren. Horretarako inklusio kriterio batzuk zehaztu ziren:

- Etxean edo ospitalean 40,5ºCko tenperatura edo altuagoa objektibatu zaion eta aurrez osasuntsu den 3 eta 24 hilabete arteko pazientea.
- Itxura ona duen pazientea, ebaluazio pediatrikorako triangeluan oinarritua.
- Odol kultura burutu zaion pazientea.

Emaitza aldagaia benetako bakterio patogeno baten identifikazioa izan zen, bai odolean burututako hazkuntza bitartez, bai meningokoko/neumokokoaren PCR tekniketan lortutako detekzio positibo baten bitartez.

Ondorengo datuak bildu ziren:

- Adina
- Sexua
- Aurrekariak
- Kontsulta egin den urte eta hilabetea
- Neumokokoaren aurkako txertaketa egoera
- Etxean erregistratu den tenperatura maximoa
- Larrialdi zerbitzu pediatrikoan neurtutako tenperatura
- Gertaera berarekin zerikusia duten aurreko eta geroko kontsulta (odol kultura lortu den gertaera eguna delarik abiapuntu)
- Balizko lotutako sintomak
- Larrialdi zerbitzu pediatrikora iristean duen egoera
- Azterketa fisikoa
- Odol probak (leukozitoen zenbaketa, neutrofiloen zenbaketa absolutua, C proteina erreaktiboa, prokaltzitonina)
- Kultura eta PCR bidezko identifikazio probak
- Toraxeko erradiografia
- Gernu eta likido zefalorrakideoan burututako probak, analisi biokimiko, kultura eta PCR bidezko identifikazio probak
- Beste proba mikrobiologiko batzuk
- Isolatu den mikroorganismoa

- Azken diagnostikoa
- Norakoa
- Bilakaera

Definizioak aurretik azaldu diren berberak dira.

Garai honetan ikerketa burutu zen larrialdi zerbitzuan, odol-kultura, leukozitoen zenbaketa, neutrofiloen zenbaki absolutua, C proteina erreaktiboa, prokalzitonina, gernu banda erreaktiboa eta pneumokokoaren eta meningokokoaren PCRa egitea gomendatzen zen jatorri argirik gabeko 40,5ºC edo altuagoa zuen 3 eta 24 hilabete arteko sukardun umeen artean, haien txertaketa egoera edozein zelarik ere. Beste proba batzuk (gernu-kultura, erradiografia,…) pazientea artatu zuen medikuaren erabakiaren arabera egin zen.

Analisi estadistikoari dagokionez, IBM SPSS Statistics for Windows programaren 23.0 bertsioa erabiliz egin zen (IBM, Armonk, New York, AEB). Aldagai kualitatiboak, maiztasun eta ehuneko absolutuak erabiliz deskribatu ziren, eta aldagai jarraikiak batezbestekoa, desbideratze estandarra edo mediana eta kuartil arteko tartea erabiliz. Aldagai kualitatiboen arteko lotura aztertzeko Chi-karratuaren proba erabili zen.

Ikerkuntza zentruanitzetan oinarritutako lanak (SEUPeko Gaixotasun Infekziosoetako Lan Taldearen baitan burututakoak)

Zentro anitza den behaketa-azterketa prospektiboa

- Gangoiti I, Zubizarreta A, Elgoibar B, Mintegi S; Infectious Diseases Working Group, Spanish Society of Pediatric Emergencies (SEUP). Occult Bacteremia in Young Children with Very High Fever Without a Source: A Multicenter Study.

Pediatr Infect Dis J. 2020 Dec;39(12):e462-e464. doi: 10.1097/INF.0000000000002891. PMID: 32898089

Zentro anitza den ikerketa prospektiboa da. Espainiako Pediatriako Larrialdietako Elkartearen Ikerketa Sareak onartutako Pediatriako Larrialdietako Medikuntzako Espainiako Elkartearen Gaixotasun Infekziosoen Lantaldearen izenean, zentro anitza den behaketa-azterketa prospektiboa burutu zen Espainiako pediatriako larrialdietako 6 zerbitzutan artatu ziren aurrez osasuntsu ziren eta 40,5ºC edo tenperatura altuagoa zuten jatorri argirik gabeko sukardun pazienteen kohorte baten oinarritua. Pazienteak prospektiboki erreklutatu ziren 2018ko urtarrilaren 1etik 2019ko abenduaren 31ra arte.

Ikerketa unizentrikoan planteatu ziren inklusio kriterioak, maneiu terapeutikoak, definizioak eta emaitza aldagaia berberak dira.

Erreklutatutako paziente guztiek, haien zainketaz arduratzen ziren medikuek Google Drive® aplikazioaren bitartez betetako galdetegi elektroniko espezifikoak zituzten eskuragarri. Ikerketa hasi orduko, parte hartuko zuten larrialdi zerbitzu guztietako arduradunei banatu zitzaizkien galdetegiak, metodoaren argitasuna bermatzeko, zalantzak argitzeko eta ondorioz, bildutako datuen kalitatea hobetzeko. Galdetegia larrialdi zerbitzutik edo ospitalizaziotik etxerako alta sinatzen zuen medikuak bete zuen, bai pazientea eta baita larrialdi zerbitzu pediatrikoaren ezaugarri eta emaitzen inguruko informazio osoa lortu asmoz. Osatutako galdetegiak ikertzaile nagusiak baino ez zituen eskuragarri.

Analisi estadistikoari dagokionez IBM SPSS Statistics for Windows programaren 23.0 bertsioa erabiliz egin zen (IBM, Armonk, New York, AEB). Aldagai kategorikoak maiztasun eta ehuneko absolutuen arabera deskribatzen dira, eta aldagai jarraikiak batezbesteko eta desbideratze estandarraren edo medianaren eta kuartil arteko tartearen

arabera. Chi-karratuaren proba erabili da aldagai kategorikoen arteko lotura aztertzeko. Hasiera baten, ikerketaren lagin osoaren helburua 500 pazientetan ezarri zen. Hala ere, kopurua 200 pazientera iritsi eta emaitzak hain esanguratsu irudituta, ikerketa unizentrikoa publikatu zuen aldizkariarekin kontaktuan jarri eta erreklutamenduarekin jarraitu edo ez (markatutako helburura iristeko gutxienez bi urte gehiago estimatu ziren) eztabaidatu zen. Emaitzek izan zezaketen garrantziagatik, erreklutamendua bertan behera utzi eta publikatzeko saiakera egiteko eskatu zitzaigun.

Erregistro prospektibo handi batetik eratorritako bigarren mailako analisien emaitza diren artikuluak

- Elgoibar B, Gangoiti I, Garcia-Garcia JJ, Hernandez-Bou S, Gomez B, Martinez Indart L, Mintegi S; Bacteremia Study Working Group from the Infectious Diseases Working Group, Spanish Society of Pediatric Emergencies (SEUP). Paediatric *Escherichia coli* bacteraemia presentations and high-risk factors in the emergency department. Acta Paediatr. 2021 Mar;110(3):1032-1037. doi: 10.1111/apa.15549. Epub 2020 Sep 9. PMID: 32815584
- Ecclesia FG, Alonso Cadenas JA, Gómez B, Gangoiti I, Hernández-Bou S, de la Torre Espí M; Bacteremia Study Working Group from the Infectious Diseases Working Group, Spanish Society of Pediatric Emergencies. Late-onset Group B *Streptococcus* Bacteremia Evaluated in the Pediatric Emergency Department and Risk Factors for Severe Infection. Pediatr Infect Dis J. 2022 Jun 1;41(6):455-459. doi: 10.1097/INF.0000000000003520. Epub 2022 May 6. PMID: 35446825.

Espainiako 23 larrialdi zerbitzutan burutu zen erregistro prospektibo baten emaitza dira artikulu hauek; aro pediatrikoan detektatzen diren bakteriemien karakterizazioa egitea helburu zuen erregistro prospektibo handi baten bigarren mailako analisien emaitza hain

zuzen ere. 2010ean, Pediatriako Larrialdietako Medikuntzako Espainiako Elkarteak, gaixotasun infekziosoen lan taldea buru, Espainiako pediatriako larrialdi zerbitzuetan isolatutako odol-kultura positiboen erregistro multizentriko prospektibo bat ezartzea proposatu zuen. Haur jaioberri eta 20 urte bitarteko pazienteak prospektiboki erreklutatu ziren 2011 eta 2016 artean. 2011n zehar, 15 pediatriako larrialdi zerbitzuk hartu zuten parte erreklutamenduan, 22k 2012an, 21ek 2013an, 19k 2014an, 17k 2015 eta 2016an.

Ikerketa hauen xederako, euren odol laginean *E. coli* eta B taldeko estreptokokoa isolatu ziren pazienteak aztertu ziren hurrenez hurren.

Definizio garrantzitsuenak gainerako ikerketetan ezarri ziren berak izan ziren. Pazientearen itxura ona ebaluazio pediatrikorako triangeluak ezarri zuen. Aurrekarietan, bakteriemia izateko arriskua areagotzen duten faktoreak kontutan hartu ziren (immunogutxiegitasuna, gaixotasun onkologikoa, dispositiboen presentzia eta bestelakoak). Sepsiaren diagnosirako Goldstein et al.ek argitaratutako irizpideak hartu ziren kontuan, sepsi larriaren kontzeptua bete zuen pazientea hala deklaratuz eta bakteriemia ezkutuaren definizioa ere bere horretan mantendu zen. B taldeko estreptokokoa ikertzea helburu zuen artikulurako, mikroorganismo honek sortutako bakteriemia berantiarra, infekzioa 7 eta 89 egun arteko haurrengan gertatu zenean definitu zen. B taldeko estreptokokoak sortutako infekzioaren arrisku-faktore gisa amaren kolonizazioa edo kolonizazio egoeraren ez ezagutzea eta 37 aste baino lehenago gertatutako erditzea finkatu ziren.

Larritasuna definitu zuten irizpideak honakoak izan ziren (gutxienez bat bete behar izan zuten): heriotza, sekuelak, Zainketa Intentsiboko Unitatean egonaldia eta konplikazio akutu larrien agertzea (besteak beste, giltzurruneko edo gibeleko gutxiegitasuna, arnas-gutxiegitasun akutuaren sindromea, iktusa, konbultsio larrien agertzea,…).

E. coli bakteriemiaren aurkezpen motak identifikatzeko, korrespondentzia anitzeko analisia eta Cluster analisia erabili ziren. Korrespondentzia anitzeko analisia egiteko aldagai kategoriko hauek erabili genituen: sexua, adina, ebaluazio pediatrikorako triangeluan oinarritutako itxura, aurrez osasuntsua izatea, sukarra, gainontzeko sintomak eta azterketa fisikoa. Aldagai batzuekin azpitaldeak eratu ziren. Adinaren kasuan, 3 hilabetetik beherako, 3-12 hilabete eta 12 hilabetetik gorako pazienteen taldeak sortu ziren. Triangeluan oinarrituta, itxura normala edo ez, alde zirkulatorioa normala edo ez eta arnasketaren aldea normala zen edo ez izatearen arabera sailkatu ziren. Ondoren, Cluster analisia egin zen. Horretarako, "a priori" heterogeneoak ziren datu multzoa talde homogeneoetan bihurtu behar da. Korrespondentzia anitzeko analisietan lortutako faktoreak aldagai gisa erabili ziren Cluster analisia egiteko eta *E. coli* bakteriemia aurkezpenen taldekatze egokia lortzeko. Clusterrak sortzeko, distantzia euklidear karratua eta Ward metodoa erabili ziren. Metodo honek korrespondentzia analisia eta Cluster analisia konbinatu zituen *E. coli* bakteriemia kasuak taldetan sailkatzeko. Laburbilduz, teknika matematiko honek, aurretiaz zehaztu gabeko talde ezberdinetan banatzen du populazioa; banatutako talde bakoitzeko pazienteak antzekoak dira euren artean, baina beste taldeekiko ezberdinak. Azkenik, Chi-karratuaren testa erabili zen larritasunaren eta *E. coli* bakteriemia aurkezpen mota ezberdinen arteko lotura aztertzeko.

B taldeko estreptokokoaren kasuan egin zen ikerketan, distribuzio normaldun aldagaiak, batez besteko eta desbideratze estandar gisa adierazi ziren eta distribuzio normalik ez zutenak mediana eta kuartil arteko tarte gisa. Normalki banatutako datuetarako, bi isatseko T probak erabili ziren taldeen arteko batezbesteko balioak konparatzeko eta Mann-Whitney U proba gainontzeko datuetarako. Aldagai kategorikoak ehunekotan adierazi ziren eta Chi-karratuaren proba erabiliz konparatu. B taldeko estreptokokoak eragindako bakteriemia identifikatzeko odolean aztertzen ziren biomarkatzaile

bakoitzaren sentikortasuna eta gaixotasun larria/ez larria bereizteko sentikortasuna kalkulatu ziren. Aldagai anitzeko erregresio logistiko bitarra egin zen prozesuaren larritasun handiagoarekin lotutako arrisku-faktore independenteak identifikatu asmoz. Aldagai bakarreko analisian, proba gehigarri gisa, atzerako ezabaketadun erregresioa burutu zen p balioa < 0,2 zuten aldagai bitar horietarako. Analisi estatistikoak kasu honetan STATA v.15 programa erabiliz egin ziren.

ETIKA

Burututako lan guztiek Etika komitearen onarpena dute, ospitalekoa edo Euskadikoa. Kodeak:

- Erregistro unizentrikoaren irekiera Ospitaleko Ikerketa Klinikoko Batzorde Etikoak baimendu zuen; txostenaren kodea E11/52 da. Pandemian burutu zen ikerketarako, berriz eskatu zitzaion baimena eta baimendutako txostenaren kodea ondorengoa da: E22/36.
- Bakteriemiaren prebalentzia ondorioztatzeko sukar oso altua duten bularretako haurrak ikertu dituen lan unizentriko eta multizentrikoa, Euskal Herriko Ikerketa Klinikorako Batzorde Etikoak baimendu zituen eta barne kodeak E16/11 eta PI2017169 izan ziren, hurrenez hurren.
- Bi azpianalisiak egin ziren odol kulturen erregistro zentruanitzaren ikerketa, Euskal Herriko Ikerketa Klinikorako Batzorde Etikoak baimendu zuen, PI2011040 barne kodearekin.

EMAITZAK

Gaur atzo baino gehiago dakit (Btx)

EMAITZAK

HELBURUREN ARABERAKO ARGITARALPENAK

Hamalau urtetik beherako pazienteetan baieztatu diren IBIen aurkezpen klinikoaren karakterizazioa egin eta haien larritasuna deskribatu

- Gangoiti I, Valle JR, Sota M, Martinez-Indart L, Benito J, Mintegi S. Characteristics of children with microbiologically confirmed invasive bacterial infections in the emergency department. Eur J Emerg Med. 2018 Aug;25(4):274-280. doi: 10.1097/MEJ.0000000000000453. PMID: 28118320.

Azterketa-aldiak iraun zituen zortzi urteetan zehar, 14 urtetik beherako pazienteei dagozkien 456.830 kontsulta erregistratu ziren larrialdi zerbitzu pediatrikoan. Horietatik 223tan IBIa (%0,048, %95 KT: 0,047-0,049) diagnostikatu zen; 187 (%83,9) ziren aurrez osasuntsu.

Gizonezkoak 126 (%56,5) izan ziren eta batez besteko adina 19 hilabetekoa izan zen (kuartil arteko tartea: 5 hilabetetik 2 urtera). Ia erdiak [102 (%45,7)] urria eta urtarrila bitartean diagnostikatu ziren (*gainontzeko ezaugarriak, ikus Table 1)*. *S. pneumoniae* [68 (%30,5)] eta *N. meningitidis*ek [42 (%18,8)] *(Ikus Table 2)*, kasuen ia %50 osatu zuten. IBI neumokozikoaren beheranzko joera ikusi zen 2008-2015 aldian, nahiz eta ondorio hau ez izan esangurantsua estadistikoki (*Ikus Figure 1*). *S. pneumoniae* 57 pazientetan serotipatu zen, horietatik 37 (%64,9) txerto 13balentearen babespean leudeke bilduta.

Pazienteen azken diagnostikoa, adina eta pazientearen ezaugarri klinikoak nabarmen aldatu ziren isolatutako bakterioaren arabera (*ikus Table 3 eta Table 4*). Guztira, 147

(%65,9) paziente izan ziren ospitaleratuak (64 zainketa intentsiboen unitatean, paziente guztien %28,7). Gehiengo zabalaren [218 (%97,8)] eboluzioa ona izan zen, nahiz eta lau kasutan (%1,8) pazientea hil egin zen eta beste 8k (%3,6) sekuela iraunkorrak pairatu. Beste 3 pazientetan deribazio bentrikuloperitoneala ahalbidetzeko dispositiboak porrot egin eta ordezkapenaren beharra izan zen.

Gaixotasunaren lehenengo 24 orduetan larrialdi zerbitzuetan artatu izana, sukarraz gain beste sintomaren baten presentzia eta larrialdi zerbitzura iristean ebaluazio pediatrikorako triangelu egonkorrik ez izatea larritasun handiagoa izateko arrisku-faktore independente definitu ziren. Espezifikotasun eta etekin diagnostikoaren kurbaren azpiko azalera 0,805ekoa (%95 KT: 0,741-0,868) izan zuen eredu honek eta Hosmer-Lemeshow probarako p balioa 0,356 izan zen.

Infekzio meningokozikoak izan ziren IBI larrienak (odds ratioa: 12,3, %95 KT: 5,3-28,4), eta baita sepsia edo meningitisa beste diagnostiko batzuen aldean (%82,1, %44 eta %7, hurrenez hurren, $p < 0,001$). IBIa larrialdietara egindako bigarren bisita batean diagnostikatu zen 32 pazientetan (%14,3), 13 *S. pneumoniae* eta 7 *N. meningitidis*. Horietatik, seik sepsia izan zuten azken diagnostiko moduan eta bat hil egin zen. Bigarren kontsultan IBIa diagnostikatu zitzaien 32 paziente horietatik lauk (%12,5) heriotza edo sekuela iraunkorrak pairatu zituzten [vs. Lehen bisitan diagnostikatu ziren 191etatik zortzitan (%4,1), $p = 0,07$].

Taulak eta figurak artikulu originaletik berreskuratuak izan dira.

Table 1: Characteristics of the patients diagnosed with an invasive bacterial infection.

	n (%)	95% CI
Sex (male)	126 (56.5)	50–63
Age: < 12 months	86 (38.6)	32.2–45
Increased risk of invasive bacterial infection		
No	187 (83.8)	78.9–88.6
Immunological and/or with central venous catheter	21 (9.5)	5.6–13.3
Others	15 (6.7)	3.4–9.9
Pneumococcal vaccine dose received		
Unknown	24 (10.8)	6.7–14.8
None	117 (52.5)	45.9–59
1 doses	9 (4)	1.4–6.5
2 doses	13 (5.8)	2.7–8.8
3 doses	29 (13)	8.5–17.4
4 doses	31 (13.9)	9.3–18.4
Duration of fever		
Afebrile	8 (3.6)	1.1–6
< 6 h	64 (28.7)	22.7–34.6
6–24 h	63 (28.3)	22.3–34.2
> 24 h	88 (39.4)	33–45.8
Symptoms		
Fever only	64 (28.7)	22.7–34.6
Respiratory	44 (19.7)	14.5–24.9
Digestive	60 (26.9)	21.1–32.7
Neurological	35 (15.7)	10.9–20.5
Rash	21 (9.4)	5.5–13.2
Osteoarticular and/or soft tissue	19 (8.5)	4.8–12.1
Others	14 (6.3)	3.1–9.5
Well appearing upon arrival at the ED	165 (74)	68.2–79.7
Physical examination		
Normal	92 (41.3)	34.8–47.7
Rash	52 (23.3)	17.7–28.8
Abnormal pulmonary auscultation	28 (12.6)	8.2–16.9
Alteration of the central nervous system	32 (14.3)	9.7–18.9
Osteoarticular and/or soft tissue findings	15 (6.7)	3.4–9.9
Others	18 (8.1)	4.5–11.6

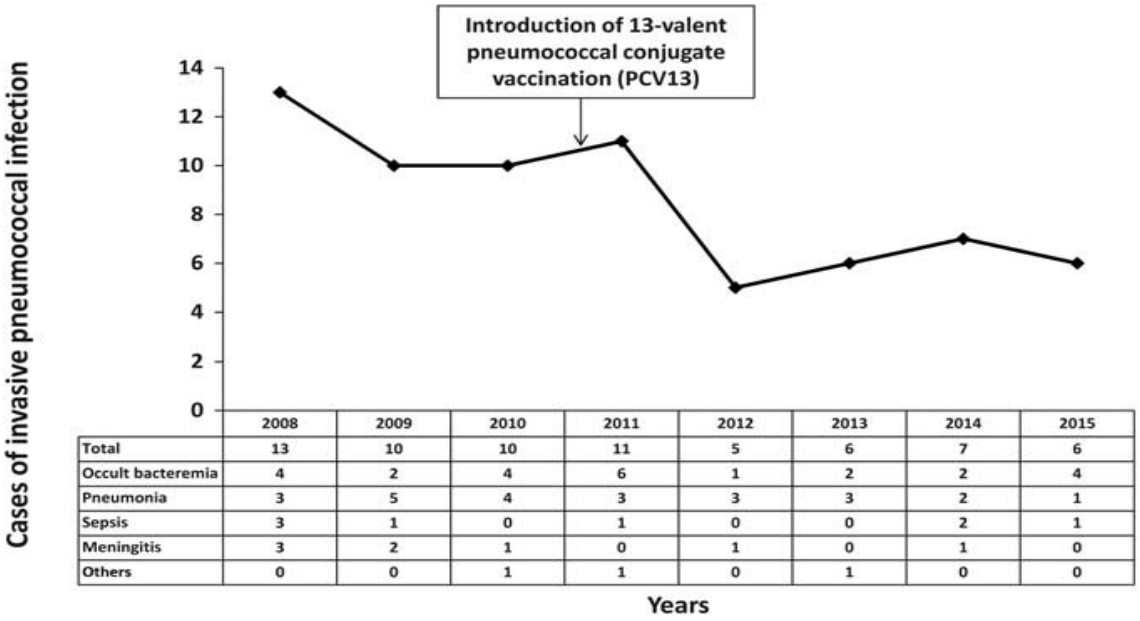
***ED**, emergency department; **CI**, confidence interval.*

Table 2. Bacteria isolated from patients with an invasive bacterial infection.

Bacteria	*n* (%)	95% CI
Streptococcus pneumoniae	68 (30.5)	24.5–36.5
Neisseria meningitidis	42 (18.8)	13.7–23.9
Escherichia coli	33 (14.8)	10.1–19.5
Staphylococcus aureus	25 (11.2)	7.1–15.3
Streptococcus agalactiae	9 (4)	1.4–6.6
Streptococcus pyogenes	9 (4)	1.4–6.6
***Staphylococcus coagulase* (−)**	8 (3.6)	1.1–6.1
Enterococcus faecalis	6 (2.7)	0.6–4.8
Others	23 (10.3)	6.4–14.4

*Data are expressed as n (%) and 95% CI; **CI**, confidence interval.*
Others: Salmonella spp. 5, Pseudomonas aeruginosa 3, Klebsiella spp. 3, Proteus mirabillis 2, Haemophilus influenzae 2, Listeria monocytogenes 1, Moraxella catharralis 1, Morganella morgagni 1, Propionebacterium acnes 1; Streptococcus mitis 1, Staphylococcus lugdunensis 1, Streptococcus salivarius 1; Campylobacter jejuni 1.

Figure 1. Cases of invasive pneumococcal bacterial infection by year.



	2008	2009	2010	2011	2012	2013	2014	2015
Total	13	10	10	11	5	6	7	6
Occult bacteremia	4	2	4	6	1	2	2	4
Pneumonia	3	5	4	3	3	3	2	1
Sepsis	3	1	0	1	0	0	2	1
Meningitis	3	2	1	0	1	0	1	0
Others	0	0	1	1	0	1	0	0

Table 3. Isolated bacteria related to the final diagnosis of the patients.

	Occult bacteraemia	Sepsis/shock	Pneumonia	Urinary tract infection	Meningitis	Arthritis/ osteomyelitis	Cellulitis/ abscess	Others	Total
Streptococcus Pneumoniae	25 (36.8)	8 (11.8)	24 (35.3)	0	8 (11.8)	0	0	3 (4.3)	68 (30.5)
	25.3–48.26	4.1–19.5	23.9–46.7		4.1–19.5			0–9.3	24.5–36.5
Neisseria meningitidis	2 (4.8)	30 (71.4)	0	0	10 (23.8)	0	0	0	42 (18.9)
	0–11.26	57.7–85.1			10.9–36.7				13.7–23.9
Escherichia coli	2 (6.1)	3 (9.1)	0	26 (78.8)	2 (6.1)	0	0	0	33 (14.8)
	0–14.2	0–18.9		64.8–92.8	0–14.27				10.1–19.5
Staphylococcus aureus	8 (32.0)	1 (4.0)	1 (4.0)	1 (4.0)	0	13 (52.0)	0	1 (4.0)	25 (11.2)
	13.7–50.3	0–11.7	0–11.7	0–11.7		32.4–71.6		0–11.7	7.1–15.3
Streptococcus agalactiae	2 (22.2)	6 (66.7)	0	0	1 (11.1)	0	0	0	9 (4)
	0–49.4	35.9–97.5			0–31.6				1.4–6.6
Streptococcus pyogenes	3 (33.3)	2 (22.2)	1 (11.1)	0	0	0	3 (33.3)	0	9 (4)
	2.5–64.1	0–49.4	0–31.6				2.5–64.1		1.4–6.6
Staphylococcus coagulase (−)	5 (62.5)	1 (12.5)	0	0	1 (12.5)	0	1 (12.5)	0	8 (3.6)
	28.9–96.0	0–35.4			0–35.4		0–35.4		1.1–6.1
Enterococcus faecalis	4 (66.7)	0	1 (16.7)	0	1 (16.7)	0	0	0	6 (2.7)
	29–100		0–46.5		0–46.5				0.6–4.8
Others	9 (39.1)	5 (21.7)	0	0	2 (8.7)	0	1 (4.3)	6 (26.1)	23 (10.3)
	19.2–59	4.8–38.5			0–20.2		0–12.6	8.1–44.1	6.3–14.3
Total	60 (26.9)	56 (25.1)	27 (12.1)	27 (12.1)	25 (11.2)	13 (5.8)	5 (2.2)	10 (4.5)	223
	21.1–32.7	19.4–30.8	7.8–16.4	7.8–16.4	7.1–15.3	2.7–8.9	0.3–4.1	1.8–7.2	

Data are expressed as n (%) and 95% CI

Table 4: Clinical characteristics of the invasive infections caused by the most common bacteria.

	***Streptococcus pneumoniae* (*n* = 68)[a]**	***Neisseria meningitidis* (*n* = 42)[b]**	***Escherichia coli* (*n* = 33)**	***Staphylococcus aureus* (*n* = 25)[c]**	***Streptococcus pyogenes* (*n* = 9)**	***Streptococcus agalactiae* (*n* = 9)**
Age (months) [median (interquartile range)] (25–75%)	19 (11.2–35)	20 (7.7–48)	1 (0–9)	84 (18–126)	39 (20–72)	0 (0–1.5)
Previously healthy	66 (97.1)	42 (100)	28 (84.8)	20 (80)	9 (100)	7 (77.8)
Duration of fever < 12 h	21 (30.9)	17 (40.5)	20 (60.6)	7 (28)	3 (33.3)	9 (100)
Fever > 39°C	53 (77.9)	28 (66.7)	12 (36.4)	13 (52)	7 (77.8)	2 (22.2)
Associated symptoms						
None	16 (23.5)	8 (19)	18 (54.5)	7 (28)	0	4 (44.4)
Respiratory	30 (44.1)	4 (9.5)	7 (21.2)	0	0	0
Rash	0	17 (40.5)	0	0	3 (33.3)	0
Neurological	13 (19.1)	13 (31)	1 (3)	1 (4)	1 (11.1)	1 (11.1)
Stable on arrival	42 (61.8)	24 (57.1)	31 (93.9)	24 (96)	7 (77.8)	6 (66.7)
Physical examination						
None	25 (36.8)	8 (19)	27 (81.8)	7 (28)	1 (11.1)	4 (44.4)
Abnormal PA	21 (30.9)	0	0	1 (4)	0	0
Rash	8 (11.8)	32 (76.2)	1 (3)	2 (8)	5 (55.6)	0
CNS alteration	14 (20.6)	2 (4.8)	3 (9.1)	0	0	4 (44.4)
Final diagnosis						
Occult bacteraemia	25 (36.8)	2 (4.8)	2 (6.1)	8 (32)	3 (33.3)	2 (22.2)
Sepsis	8 (11.8)	30 (71.4)	3 (9.1)	1 (4)	2 (22.2)	6 (66.7)
Pneumonia	24 (35.3)	0	0	1 (4)	1 (11.1)	0
Urinary infection	0	0	26 (78.8)	1 (4)	0	0
Meningitis	8 (11.8)	10 (23.8)	2 (6.1)	0	0	1 (11.1)
OAI	0	0	0	13 (52)	3 (33.3)	0
Others	3 (4.4)	0	0	1 (4)	0	0
Evolution						
Death	2 (2.9)	0	0	0	1 (11.1)	0
Sequelae	5 (7.4)	3 (7.1)	0	0	0	0

***CNS**, central nervous system; **OAI**, osteoarticular and/or soft tissue infection; **PA**, pulmonary auscultation.*
[a]Occult bacteraemia and meningitis were more common in children aged younger than 2 years (21/25, 84%; and 6/8, 75%, respectively). Most pneumonia cases were found in children aged older than 2 years (16/24; 66%).
[b]The presence of rash varied depending on the final diagnosis for the patient (29 of 30 patients (96.7%) with a final diagnosis of sepsis showed rash compared with 2/10 (20%) with meningitis, P < 0.0001).
[c]One of these was methicillin resistant.

- Gangoiti I, Gangoiti I, Gorostizaga Z, Aranzamendi M, Gomez B, Benito J, Mintegi S. Repeated Emergency Department Visits Among Children with Invasive Bacterial Infections. Pediatr Infect Dis J. 2021 May 1;40(5):e205-e207. doi: 10.1097/INF.0000000000003062. PMID: 33464016

Azterketa-aldiak iraun zituen hamabi urteetan zehar, 14 urtetik beherako pazienteei dagozkien 601.902 kontsulta erregistratu ziren larrialdi zerbitzu pediatrikoan eta horietatik 342ri IBIa diagnostikatu zitzaien.

Horietatik 70 ez ziren aurrez osasuntsu eta paziente bat bihotz birika geldialdian sartu zenez larrialdi zerbitzuan (*S. pyogenes*ek eragindako shock septiko baten ondorioz hil egin zen pazientea) ez genuen analisian sartu. Orotara, aurrez osasuntsu ziren 271 pazientetan burutu genuen analisia.

Bataz besteko adina 15 hilabetekoa zen (kuartil arteko tartea 5 eta 43 hilabete artekoa; eta 118 (%43,5) emakumeak ziren. Ehun eta laurogeita hemeretzi pazientek (%73,4) antibiotiko parenterala jaso zuten lehen bisitan. Antibiotiko parenteralik jaso ez zuten pazienteen lehenengo eta bigarren bisitaren arteko denboraren mediana 36 ordukoa izan zen (24-48 ordu arteko kuartil arteko tartea) *(ikus Table 1)*. Hamabost pazientetan larritasun irizpideak objektibatu ziren: 3 hildako eta sekuela iraunkorrak garatu zituzten beste 12 paziente. Hauen artean: 5 neurologiko (deribazio bentrikuloperitoneala ahalbidetzen duen gailuaren porrota eta haren ordezkapena, hidrozefalia, gorreria eta epilepsia), 3 osteoartikular (protesi beharra, herren iraunkorra eta anputazio txikiak), bi pazientetan giltzurrun-gutxiegitasun kronikoa (horietako batek giltzurrun-transplantea behar izan zuen), bi pazientetan arnas-gutxiegitasun murriztaile kronikoa eta sekuela kardiologiko larria izan zuen beste paziente bat (hainbat balbularen ordezkapenaren

beharra). Larritasun irizpide hauek bete zituzten 15 paziente hauetatik, 7k ez zuten antibiotikorik jaso lehen bisitan (2 heriotza, 5 paziente sekuela iraunkorrekin). Larritasun irizpidea gehiago eman zen antibiotikoa bigarren kontsultan jaso zuten pazienteen artean (%9,8 vs %4, p = 0,07). Larritasun irizpideak betetzen zituzten pazienteen tasa pairatutako IBI motaren arabera ezberdina izan zen: 9kasu/61 sepsiko (%14,8; [%95 KT], 7-26,2), 3kasu/36 meningitisen artean (%8,3; %95 KT, 1,7-22,5), 3kasu/119 infekzio fokal inbaditzaileko (%2,5; %95 KT, 0,5-7,2) eta larritasun irizpidedun pazienterik ez bakteriemia ezkutua diagnostikatu zen taldean. Tasa hau ez zen aldatu bisiten arteko denbora tartearen arabera.

Taula artikulu originaletik berreskuratua izan da.

Table 1. Characteristics of previously healthy patients with an invasive bacterial infection in relation to the administration or non-administration of parenteral antibiotic on the first visit to the emergency department.

	Parenteral antibiotic administered in the first ED visit		
	Yes; n=199	**No; n=72**	**p**
Age (months)	15 (5-43)	14 (4-42)	n.s
Sex (female)	87 (43.7%)	31 (43.1%)	n.s
Season			
Spring	33 (16.6%)	21 (29.2%)	
Summer	31 (15.6%)	16 (22.2%)	<0.01
Autumn	68 (34.2%)	19 (26.4%)	
Winter	67 (34.2%)	16 (22.2%)	
Fever: yes	195 (98%)	59 (81.9%)	<0.01
Duration of fever (hours)	12 (5-32)	12 (8-48)	n.s
Not well-appearing upon the arrival to the ED	56 (28.1%)	2 (2.8%)	<0.01
No other symptom except fever	58 (29.1%)	33 (45.9%)	0.01
Digestive	44 (22.1%)	11 (15.3%)	
Respiratory tract and ORL	37 (18.6%)	18 (25%)	
Neurologycal	37 (18.6%)	3 (4.2%)	
Exanthema	22 (11.1%)	2 (2.8%)	
Joint/soft tissue	17 (8.5%)	7 (9.7%)	
Normal physical exam	72 (36.2%)	51 (70.8%)	<0.01
Other signs			
Exanthema	50 (25.1%)	6 (8.3%)	
Neurologycal	38 (19.1%)	2 (2.8%)	
Respiratory tract and ORL	28 (14.1%)	11 (15.3%)	
Joint/soft tissue	17 (8.5%)	2 (2.8%)	
Isolated microorganism			n.s.
S. pneumoniae	60 (30.2%)	24 (33.3%)	
N. meningitidis	47 (23.6%)	10 (13.9%)	
S. aureus	20 (10.1%)	14 (19.4%)	
E. coli	31 (15.5%)	7 (9.7%)	
S. agalactiae	11 (5.5%)	1 (1.4%)	
Others	30 (15.1%)	17 (22.3%)	
Final diagnosis			n.s.
Sepsis	47 (23.6%)	14 (19.4%)	
Meningitis	28 (14.1%)	8 (11.1%)	
Occult bacteremia	36 (18.1%)	19 (26.4%)	
Focal infection with bacteremia	88 (44.2%)	31 (43.1%)	
urinary tract infection	28 (14.1%)	4 (5.6%)	
pneumonia	24 (12.1%)	8 (11.1%)	
osteoarticular or soft tissue infection	19 (9.5%)	12 (16.7%	
others	17 (8.5%)	7 (9.7%)	
Severe outcome	8 (4%)	7 (9.7%)	0.07

Hamalau urtetik beherako pazienteen IBIak identifikatzeko egiten diren ohiko odol testen (leukozitoen zenbaketa, neutrofiloen zenbaki absolutua, proteina C erreaktiboa eta prokaltzitonina) balioa analizatu

- Gangoiti I, Fernandez C-L, Gallego M, Gomez B, Benito J, Mintegi S. Markers for invasive bacterial infections in previously healthy children. Am J Emerg Med. 2021 Apr 13;48:83-86. doi: 10.1016/j.ajem.2021.04.018.

Azterketa-aldiak iraun zituen hamahiru urteetan zehar, 14 urtetik beherako pazienteei dagozkien 665.997 kontsulta erregistratu ziren larrialdi zerbitzu pediatrikoan eta horietatik 367ri (%0,05) IBIa diagnostikatu zitzaien. Horietatik 286 (%77,9) ziren aurrez osasuntsu eta hauek izan ziren artikuluan analizatutako pazienteak.

Ehun eta hirurogei (%55,9) gizonezkoak izan ziren eta batez besteko adina 14 hilabetekoa (kuartil arteko tartea 5-42). Berrehun pazientek ebaluazio pediatrikorako triangelu egonkorra (%69,9) izan zuten larrialdi zerbitzura iritsitakoan, eta horietatik 95etan azterketa fisikoa normala izan zen.

Azken diagnostikoak sepsia 64 (%22,4), meningitisa 38 (%13,3), bakteriemia ezkutua 63 (%22,0) eta infekzio fokal inbaditzailea 121 (%42,3) (arnas aparatuko infekzioa 46, gernu-aparatuko infekzioa 33, infekzio osteoartikularra edo ehun bigunetako infekzioa 33 eta beste batzuk 9) izan ziren. Isolatutako bakterio ohikoenak *Streptococcus pneumoniae* 89 (%31,1*), Neisseria meningitidis* 61 (%21,3), *Escherichia coli* 40 (%14) eta *Staphylococcus aureus* 36 (%12,6) izan ziren (gainontzekoak 60, %21).

Berrehun eta hamar pazientek (%73,4) parenteralki jaso zuten antibiotikoa larrialdi zerbitzura egin zuten lehen bisitan artatuak izan zirenean. Guztira, hiru paziente hil ziren eta 14k sekuela iraunkor larriak pairatu zituzten.

Leukozitoen zenbaketa eta neutrofiloen zenbaki absolutua 284 pazientetan (%99,3) egin zen, C proteina erreaktiboa 283tan (%99,0) eta prokaltzitonina 228tan (%79,7). Prokaltzitoninarik egin gabeko paziente gehienak ikerketaren lehen bi urteetakoak dira gehienbat (zerbitzuaren baliabide sortaren barne, prokaltzitoninaren inklusio fasea) edo neumonia diagnostikatu zitzaien pazienteak (ez zegoen protokolizatua bere eskaera neumoniaren maneiu terapeutikoan).

Oro har, 265ek (%92,7) gutxienez odol-balio anormal bat izan zuten. Proba bakoitzaren sentikortasuna honakoa izan zen: prokaltzitonina %70,1 (%95 KT: 63,9-76,0), C proteina erreaktiboa %78,1 (%95 KT: 72,9-82,5), leukozitoen zenbaketa %52,8 (%95 KT: 47,0-58,6) eta neutrofiloen zenbaki absolutua %47,9 (95% KT: 42,1-53,7). Gainera, leukozitoen zenbaketa anormalen %85,2 (%95 KT: 78,7-90) leukozitosiari zegokion eta neutrofiloen zenbaki absolutu anormalaren %99,5 (%95 KT: 97,1-100) neutrofiliari. Leukopenia ez zen izan maizen egiten zen aurkikuntza, sepsiaz diagnostikatu ziren pazienteetan izan ezik [%22,2 (%95 KT: 13,7-33,9)].

Odol markatzaile bakoitzaren sentikortasuna azken diagnostiko eta bakterio eragilearen arabera aldatu zen *(Ikus Figure A eta Figure B)*. Sepsi eta meningitisaren kasuan prokaltzitonina eta C proteina erreaktiboaren sentikortasuna handiagoa izan zen; infekzio fokal inbaditzaileetan C proteina erreaktiboarena; meningokokoaren kasuan prokaltzitonina eta *S. aureus*aren kasuan C proteina erreaktiboaren sentikortasuna.

Infekzio neumokozikoei dagokienean, odoleko markatzaileen sentikortasuna ez zen aldatu txerto-egoeraren arabera. Bakteriemia ezkutu neumokozikoa diagnostikotzat jaso zuten 3 eta 24 hilabete bitarteko adineko haurren odol-markatzaile bakoitzaren sentikortasuna hauxe izan zen: prokaltzitonina %43,5 (%95 KT: 25,6-63,2); C proteina

erreaktiboa %48,3 (%95 KT: 31,4-65,6); leukozitoen zenbaketa %75,9 (%95 KT: 57,8-87,8); neutrofiloen zenbaki absolutua %58,6 (%95 KT; 40,7-74,5).

Hogeita bat pazientetan (%7,3) odol markatzaileen balioak normalak izan ziren. Paziente horien batez besteko adina 2 hilabetekoa izan zen (kuartil arteko tartea 1-11 hilabete) eta, bi pazientetan izan ezik, guztiek ebaluazio pediatrikorako triangelu egonkorra izan zuten artatuak izan zirenean. Azken diagnostikoari dagokionez, bakteriemia ezkutua izan zen 11 pazientetan (%52,4), meningitisa 4tan (%19) eta infekzio fokal inbaditzailea beste 6tan (%28,6). Guztiek bilakaera ona izan zuten.

Figura artikulu originaletik berreskuratua izan da.

Figure A. Sensitivity of the tests related to the final diagnosis.

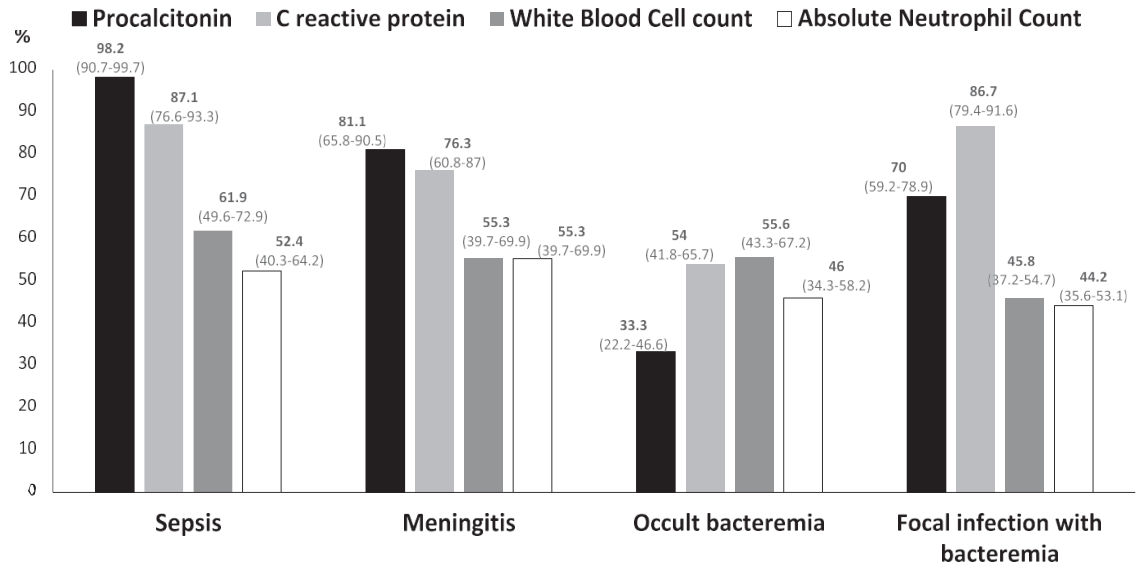
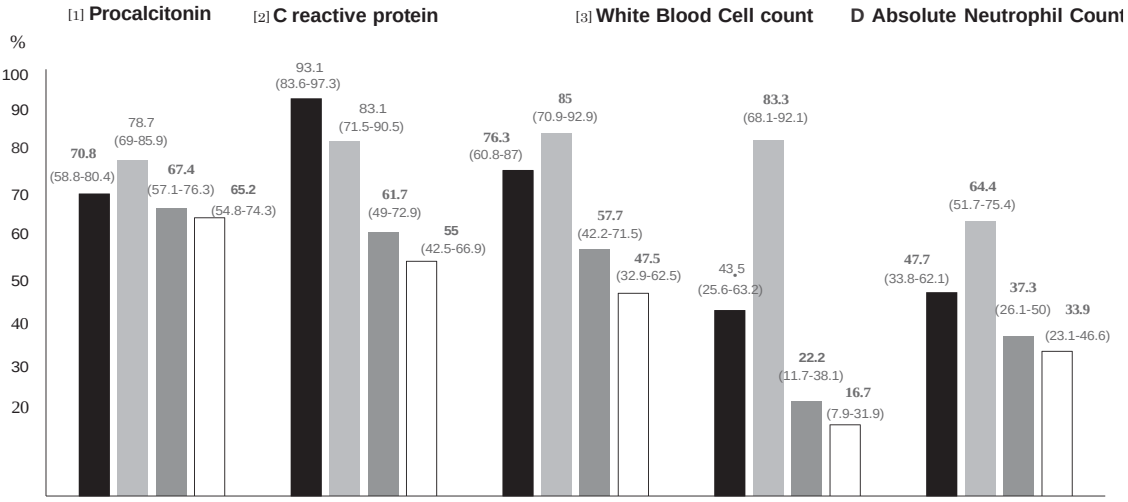


Figure B. Sensitivity of the tests related to the causative bacterium.



Rate of patients with procalcitonin >0.5 ng/ml, C reactive protein>20 mg/L, white blood cell count less than 5000 or higher than 15000/mm3; absolute Neutrophil Count less than 1,500 or higher than 10,000/mm3. 95% Confidence intervals in brackets.

Fokurik gabeko sukarra duten eta larrialdi zerbitzura egonkor iristen diren 3-24 hilabete arteko haurrak artatzerakoan odol testik ez erabiltzearen gomendioa ebaluatu

- Gangoiti I, Rodriguez E, Zubizarreta A, Benito J, Mintegi S. Prevalence of Occult Bacteremia in Infants With Very High Fever Without a Source. Pediatr Infect Dis J. 2018 Nov;37(11):e271-e273. doi: 10.1097/INF.0000000000001955. PMID: 29462106.

Ikerketa luzatu zen aldian, aurretiaz osasuntsu ziren 3 eta 24 hilabete arteko haurren 543 odol kultura eskuratu ziren 40,5ºC-ko tenperatura edo altuago zuten haurren odol laginetatik *(ikus Fugure 1)*. Ondoren, sukarraren jatorria ezagun edo ezezaguna izatearen araberako analisia egin zen. Jatorri argirik gabeko sukarra zuten 363 haurren artean batez besteko adina 13,9 ± 4,9 hilabetekoa zen, eta 189 (%52,1) emakumezkoak ziren. Neumokokoaren aurkako txertaketa ezezaguna izan zen 23tan (%6,3), eta 51k (%14) ez zuen dosirik jaso. Sukarraren iraupena 48 ordutik beherakoa izan zen 297tan (%81,8). Jasotako diagnostiko ohikoenak fokorik gabeko sukarra 282 (%77,7), gernu-infekzioa 36 (%9,9), sukarra azaleko rasharekin 16 (%4,4), neumonia 13 (%3,6) eta bakteriemia ezkutua 4 (%1,1) izan ziren. Paziente guztiek bilakaera ona izan zuten.

Talde honetan bakteriemia ezkutuaren prebalentzia %1,1 (%95 KT: 0-2,2) kalkulatu zen. Hiru bakteriemia ezkutu, neumokozikoak izan ziren (16 hilabeteko haur batek ez zuen neumokokoaren aurkako txertorik jaso; beste paziente biak txertaketa eguneratuta zuten 16 hilabete eta 19 hilabeteko bi neska ziren. Bakteriemia ezkutu neumokozikoaren prebalentzia %0,82 zela kalkulatu zen (%95 KT: 0-1,8). B motakoa ez zen *H. influenzae*k eragindako bakteriemia zuen 12 hilabeteko haur bat ere diagnostikatu zen *(ezaugarriak ikusteko ikus Supplementary table)*.

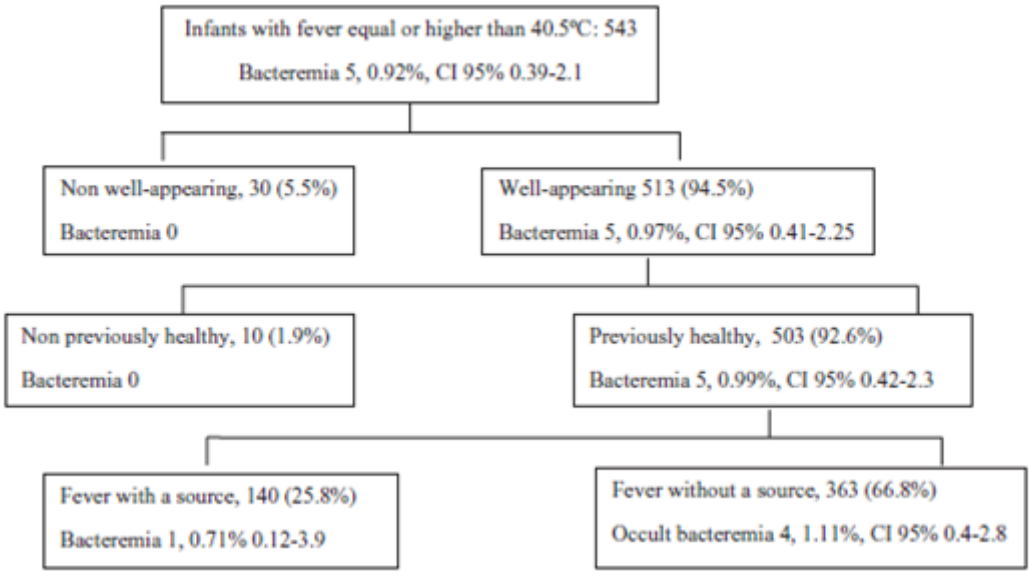
Paziente bat bera ere ez zen ospitaleratua izan (horietako hiruk muskulu barneko zeftriaxona dosi bat jaso zuten odol biomarkatzaileen anomalien ondoriozko gomendioa medio) eta guztien eboluzioa ona izan zen.

Gutxienez txerto antineumokozikoaren dosiren bat jaso zuten 289 haur horien artean, bitan bakteriemia neumokozikoa diagnostikatu zen (%0,69; %95 KT: 0-1,6).

Ikerketa-aldian, aurretiaz osasuntsu ziren beste 140 haurren odol-kulturak jaso ziren; kasu honetan jatorria ezaguna izan zitekeen; gehienek arnasketa sistemarekin erlazionatutako sintomak eta sintoma otorrinolaringologikoak zituzten. Talde honetan, *Streptococcus pneumoniae*rentzat positiboa izan zen kultura bat identifikatu zen; txertaketa kanpaina eguneratuta zeukan eta mastoiditisa diagnostikatu zitzaion 19 hilabeteko pazienteari.

Figura eta taula artikulu originaletik zuzenean berreskuratuak izan dira.

Figure 1: Patient Flow-Chart.



Supplementary table. Characteristics of the 4 patients with occult bacteremia.

Age and gender	Pneumo-coccal vaccine	Fever time	WCB	ANC	CRP	PCT	Micro-organism isolation	Antibiotic	Reconsult / destina-tion	Bacteria
12; male	complete	24	25100	20100	57	0.3	Blood culture	Ceftriaxone	No	*H. influenzae*
16; female	Three doses	96	15400	8800	0.2	0.1	Only PCR	No	Yes/ward admition	*S. pneumoniae*
19; female	Three doses	24	11800	8400	34.9	1.1	Only PCR	Ceftriaxone	Called by ED/ward admition	*S. pneumoniae*
16; female	None	1	16200	12100	3.2	4.2	PCR and blood culture	Ceftriaxone + amoxiciline	Telephone control	*S. pneumonia (15c)*

***Age** (months); **fever time** (hours); **WBC**, white blood cells count; **ANC**, absolute neutrophils count; **CRP**, C reactive protein; **PCT**, procalcitonine.*

- Gangoiti I, Zubizarreta A, Elgoibar B, Mintegi S; Infectious Diseases Working Group, Spanish Society of Pediatric Emergencies (SEUP). Occult bacteremia in young children with very high fever without a source: a multicenter study. Pediatr Infect Dis J. 2020 Dec;39(12):e462-e464. doi: 10.1097/INF.0000000000002891.

Ikerketak iraun zituen bi urteetan, 344.500 kontsulta erregistratu ziren pediatriako sei larrialdi zerbitzutan. Horietatik 203, 40,5ºC edo tenperatura altuagoa objektibatu zitzaien 3 eta 24 hilabete bitarteko haurrak dira. Batez besteko adina 14 ± 4,6 hilabetekoa zen eta 110 (%54,2) gizonezkoak ziren.

Berrehun pazientek (%98,5), neumokokoaren kontrako txertoaren dosi bat jasoa zuten gutxienez eta 103 kasutan (%50,7) sukarraren eboluzioa 24 ordu baino laburragoa izan zen.

Hogeita hamaika (%15,3, %95 KT: 11,0-20,9) pazientetan larria izan daitekeen infekzio bakterianoa diagnostikatu zen: gernu-infekzioa 14 (%6,9), neumonia 11 (%5,4) eta bakteriemia 6 (%3).

Orokorrean erabiltzen diren odol biomarkatzaileak (C proteina erreaktiboa, prokaltzitonina, leukozitoen zenbaketa eta neutrofiloen zenbaki absolutua) 192 umetan egin ziren. Hogeita hamar pazientetan (%15,6) balioak normalak izan ziren, gerora neumonia eta gernu infekzio bat diagnostikatu zitzaien paziente bi kontutan hartuta. Ziztada lunbarra 3 pazientetan egin zen (kultura negatiboak); gernu-banda erreaktiboa 169tan (%83,3), gernu-kultura 75etan (%36,9) eta toraxeko erradiografia 97tan (%47,7) *(ikus Table 1)*.

Bakteriemia ezkutuarekin diagnostikatu ziren haur guztiek odol markatzaileren baten balio anormal bat izan zuten gutxienez (sentikortasuna %100, %95 KT: 51,7-100;

espezifikotasuna: %16,1, %95 KT: 11,3-22,4; Balio prediktibo positiboa: %3,7, %95 KT: 1,5-8,2).

Bakteriemia ezkutua diagnostikatu zitzaien 6 haurretatik 3tan neumokokoa isolatu zen; bakteriemia ezkutu neumokozikoaren prebalentzia %1,48 (%95eko KT: 0,5-4,3) zela kalkulatu zen. Bakteriemia ezkutuarekin diagnostikatu ziren paziente guztien eboluzioa ona izan zen *(ikus table 2)*.

Taulak artikulu originaletik zuzenean berreskuratuak izan dira.

Table 1. Epidemiological and clinical characteristics, complementary tests, management and disposition of the patients included (n=204).

Age (in months) *	14 (9.4-18.6)
Sex (male)	111 (54.4%)
Updated vaccination status	200 (98%)
Duration of the fever (in hours)*	42 (8-76)
Blood culture performed	204 (100%)
White blood cell count performed	201 (98.5%)
Absolute neutrophil number performed	201 (98.5%)
Serum C-reactive protein performed	203 (99.5%)
Procalcitonine performed	197 (96.6%)
Urine dipstick performed	170 (83.3%)
Urine culture performed	75 (36.8%)
Chest X-ray performed	97 (47.5%)
Lumbar puncture performed	3 (1.5%)
Administered Antibiotic	126 (61.8%)
Admitted in first consultation	15 (7.4%)
Exitus or sequelae	0

Data are expressed as n and percentage
** Age and evolution time are expressed as median and interquartile range.*

Table 2. Characteristics of patients diagnosed with bacteremia.

	Age (months)	Sex	Fever time (hours)	Updated vaccination/ PCV status	WBC	ANC	CRP	PCT	Antibiotic received	Bacteria
1	13	F	18	Yes/3 doses	18400	9300	75.9	0.23	Yes. Ceftriaxone	*S. pneumoniae*
2	14	M	48	Yes/3 doses	16800	12000	259.1	9.52	Yes. Ceftriaxone	*H. influenza no b*
3	11	F	24	Yes/3 doses	24600	13100	31.83	3.10	Yes. Ceftriaxone	*S. pneumoniae*
4	13	F	18	Yes/2 doses	9400	6100	320	32	Yes. Ceftriaxone	*N. meningitidis*
5	16	M	20	Yes/3 doses	25700	22200	66	5.96	Yes. Ceftriaxone	*S. pneumoniae*
6	23	F	48	Yes/3 doses	18500	11100	77.5	0.19	Yes. Ceftriaxone	*Moraxella spp*

***WBC**, white blood cells count; **ANC**, absolute neutrophils count; **CRP**, C reactive protein; **PCT**, procalcitonine; **F**, Female; **M**, Male.*

*E. coli*k eragindako infekzio inbaditzaileen aurkezpena deskribatu eta balizko profilak eta larritasunarekiko balizko harremana ikertu

- Elgoibar B, Gangoiti I, Garcia-Garcia JJ, Hernandez-Bou S, Gomez B, Martinez Indart L, Mintegi S; Bacteremia Study Working Group from the Infectious Diseases Working Group, Spanish Society of Pediatric Emergencies (SEUP). Paediatric *Escherichia coli* bacteraemia presentations and high-risk factors in the emergency department. Acta Paediatr. 2021 Mar;110(3):1032-1037. doi: 10.1111/apa.15549. Epub 2020 Sep 9. PMID: 32815584.

Ikerketa luzatu zen garaian guztira 3.936.827 kontsulta burutu ziren parte hartu zuen larrialdi zerbitzuetan; horietatik 1.696tan benetako bakteria patogeno bat isolatu zen pazienteen odol-laginean (%0,04, %95 KT: 0,04-0,05). Horietatik 291n (%17,6, %95 KT:15,4-19,0), *E. coli* isolatu zen *(ezaugarriak ikusteko, ikus Table 1)*.

Jasotako diagnosiak ondokoak izan ziren: gernu bidetako infekzio inbaditzailea 206 kasutan (%70,8); bakteriemia ezkutua 27tan (%9,3); sepsia 32tan (%11, horietako hirutan meningitisa ere diagnostikatu zen); meningitisa 5etan (%1,7); kateterrarekin lotutako odol-infekzioa 6tan (%2,1); eta gainontzekoak beste 15 (%5,1) kasutan. Berrogeita hiru kasuk larritasun irizpideak bete zituzten (%14,8, %95 KT: 11,2-19,3) eta horietatik bi hil egin ziren *(ikus Table 2)*.

Korrespondentzia anitzeko analisi eta Cluster analisiek *E. coli* bakteriemiaren lau aurkezpen pediatriko mota nagusi identifikatu zituzten *(ikus Table 3)*. Lehen bi taldeak aurrez osasuntsu eta itxura ona zuten urtebetetik beherako haurrek osatu zituzten, gernu-bideetako infekzio inbaditzailearekin erlazionatuta zeuden eta desberdintasun nagusia adina eta sexua izan ziren. Lehen taldean hiru hilabetez azpiko gizonezkoak zeuden

nagusiki eta bigarrenean 3-12 hilabete bitarteko emakumeak. Bilakaera orokorra ona izan zen, larritasun-tasak %5,3 eta %3,1 izan ziren hurrenez hurren. Aurrez osasuntsu ez ziren 12 hilabetetik gorako pazienteek osatzen zuten hein handi batean hirugarren taldea. Azken taldean adin ezberdinetako pazienteak zeuden; herena ez zen aurrez osasuntsu eta ebaluazio pediatrikorako triangeluaren arabera egonkor ez zeudenen proportzioa handiagoa zen gainontzeko taldeekin konparatuta. Bi talde horiek ez zeuden gernu-bideetako infekzio inbaditzaileekin hain erlazionatuta eta larritasun-tasak nabarmen handiagoak izan ziren, %15 eta %50,9 hurrenez hurren ($p<0,01$). Hildako bi pazienteak azken taldean sartu ziren.

Zortzi haurri meningitis bakterianoa diagnostikatu zitzaien (horietako hirutan sepsia ere diagnostikatu zen), guztiak 5 hilabete baino gazteagoak *(ikus table 4)*. Hilabete batetik beherako *E. coli*ak eragindako bakteriemietan aurkitu zen meningitis tasa %9,4koa izan zen eta hilabete eta bi hilabeteko haurren artekoa %2,6koa izan zen. Bi hilabetetik gorako paziente bakarrean diagnostikatu zen meningitisa.

Taulak artikulu originaletatik berreskuratuak izan dira zuzenean.

Table 1. Epidemiological and clinical characteristics, complementary tests, management and disposition of the patients with *E. coli* bacteremia.

Age (in months) *	3 (1-11)
Sex (female)	131 (45%)
Non- previously healthy patients	67 (23%)
Immunosuppression	27 (9.3%)
Patients with multiorgan syndromes or systemic illness	16 (5.4%)
Serious kidney or urinary malformations	13 (4.5%)
Presence of a mechanical device	7 (2.4%)
Invasive diagnostic or therapeutic procedure in the previous 10 days	4 (1.4%)
Duration of the fever (in hours) *	12 (3-24)
Temperature upon arrival to the emergency department (°C) **	37.9 ± 1.0
Well appearing upon arrival to the emergency department	244 (83.8%)
No findings in the physical examination	226 (77.7%)
Urine culture performed	263 (90.4%)
Lumbar puncture performed	71 (24.4%)
Chest X-ray performed	33 (11.3%)
Administered Antibiotic	284 (97.6%)
Admission toward /Intensive Care Unit	255 (87.6%)

Data are expressed as n and percentage.
***** *Age and evolution time are expressed as median and interquartile range.*
****** *Temperature is expressed as mean ± standard deviation.*

Table 2. Number of patients with each severity criteria.

Severity criteria	N (%)
Sepsis	32 (11.0%)
Admission to the Intensive Care Unit *	22, 7.6%
Acute complications	8, 2.7%
Meningitis	8, 2.7%
Sequelae	7, 2.4%
Death	2, 0.7%

Data are expressed as n and percentage.
Twenty patients (6.9%) presented a single severity criteria; Sixteen patients (5.5%) presented two severity criteria; Seven patients (2.4%) presented three or more severity criteria.
***** *There are no patients with this severity criteria exclusively.*

Table 3. Main types of pediatric *E. coli* bacteremia presentations.

Variable		A (n=113, 38.8%)	B (n=65, 22.3%)	C (n=60, 20.6%)	D (n=53, 18.2%))	p value
Sex	Female	21 (18.6%)	57 (87.7%)	36 (60%)	17 (32.1%)	<0.001
Age	<3 months	95 (84.1%)	10 (15.4%)	3 (5%)	24 (45.3%)	<0.001
	3-12 months	18 (15.9%)	55 (84.6%)	6 (10%)	15 (28.3%)	
	>12 months	0	0	51 (85%)	14 (26.4%)	
Previously healthy	No	3 (2.7%)	0	47 (78.3%)	17 (32.1%)	<0.001
Fever*	Yes	88 (77.9%)	65 (100%)	58 (96.7%)	41 (77.4%)	<0.001
Other symptoms	Yes	24 (21.2%)	40 (61.5%)	30 (50%)	45 (84.9%)	<0.001
PAT**	Altered appearance	1 (0.9%)	1 (1.5%)	2 (3.3%)	35 (66%)	<0.001
	Altered Circulation	1 (0.9%)	0	1 (1.7%)	18 (34%)	
	Altered breathing	0	0	0	6 (11.3%)	
Physical exam	Altered	7 (6.2%)	5 (7.7%)	8 (13.3%)	45(84.9%)	<0.001
Associated UTI	Yes	96 (85%)	64 (98.5%)	30 (50%)	16 (30.2%)	<0.001

***** *Temperature higher than 38ºC at home and/or at the emergency department.*
****Pediatric assessment triangle.*
Data are expressed as n and %. The p values demonstrate the differences between groups among the analyzed variables.

Table 4. Rate of associated meningitis in febrile infants with *E. coli* bacteremia related to the age.

Group of age	Rate of bacterial meningitis
< 1 month old	6/64, 9.4%, 95% CI 4.4-19
1 <= months < 2	1/38, 2.6%, 95% CI 0.5-13.5
2 <= months < 3	0/30, 0, 95% CI 0-11.3
3-24 months old	1/107, 0.9%, 95% CI 0.2-5.1

Data are expressed as n, percentage and confidence interval.
***CI**, confidence interval.*

B taldeko estreptokokoak eragindako infekzio inbaditzailearen aurkezpena deskribatu eta haren larritasunarekiko balizko harremana ikertu

- Ecclesia FG, Alonso Cadenas JA, Gómez B, Gangoiti I, Hernández-Bou S, de la Torre Espí M; Bacteremia Study Working Group from the Infectious Diseases Working Group, Spanish Society of Pediatric Emergencies. Late-onset Group B *Streptococcus* Bacteremia Evaluated in the Pediatric Emergency Department and Risk Factors for Severe Infection. Pediatr Infect Dis J. 2022 Jun 1;41(6):455-459. doi: 10.1097/INF.0000000000003520. Epub 2022 May 6. PMID: 35446825.

Datu orokorrak aurreko artikulu beretik ondorioztatutakoak dira. Guztira, B taldeko estreptokokoa 134 pazientetan (%7,9, %95 KT: 6,6-9,2) hazi zen eta 118tan (%88,1) definitu zen B taldeko estreptokokoak eragindako bakteriemia berantiarra *(ezaugarriak ikus Table 1)*.

Hamazazpi (%14,4) pazientetan arrisku faktoreren bat identifikatu zen: amaren kolonizazioa edo kolonizazio egoera ezezaguna izatea 10 kasutan gertatu zen, 5 kasutan haurra goiztiarra izan zen eta bi pazientek bi arrisku faktoreak izan zituzten. Amaren kolonizazio egoera ezezaguna zen bi haur goiztiarrek ez zuten erditze lanetan antibioterapiarik jaso eta biek sepsi berantiar bat garatu zuten.

Odoleko markatzaileen balioei dagokienez, leukozitoen zenbaketa eta neutrofiloen zenbaki absolutua paziente guztietan burutu zien, C proteina erreaktiboa 117tan (%99,2) eta prokaltzitonina 93tan (%78,8). Orotara, 91k (%77,1ek) gutxienez balio anormal bat izan zuten. Proba bakoitzaren sentsibilitatea ondokoa izan zen: prokaltzitonina %80,6 (%95 KT: 71,1-88,1), leukozitoen zenbaketa %44,1 (%95 KT: 34,9-53,5), neutrofiloen

zenbaki absolutua %34,7 (%95 KT: 26,2-44,1) eta C proteina erreaktiboa %27,4 (%95 KT: 19,5–36,4). Infekzio larria diagnostikatzeko odol markatzaile ezberdinen analisien sentikortasunari dagokionez ez da esangura estatistikorik aurkitu nahiz eta prokaltzinoninaren 0,5ng/ml baino balio handiagoak infekzio larrietan maizago aurkitu *(ikus table 2)*.

Azken diagnostikoa sepsia izan zen 66 pazientetan (%55,9; hauetako 11 meningitisarekin), bakteriemia ezkutua 40tan (% 33,9), meningitisa 8tan (%6,8); infekzio fokal inbaditzailea 4tan (%3,4; bitan infekzio osteoartikularra eta beste bitan gernu-bidetako infekzioa).

Oro har, 74k (%62,7) infekzio larri bat izan zuten, horietatik 15ek izan zuten soilik ebaluazio pediatrikorako triangelu egonkorra larrialdi zerbitzuan artatuak izan zirenean. Aldagai anitzeko ereduan oinarrituta, esanahi estatistikoa lortu zuen infekzio larriarekin lotutako oinarrizko arrisku-faktore bakarra, triangeluan oinarritutako egoera ez egonkorra izan zen *(ikus table 3)*.

Ospitaleratzea 115 pazientetan egin zen, horietako 35 (%29,7) zainketa intentsiboen unitatean. Zainketa intentsiboen unitatean ingresatuak izatearekin lotutako oinarrizko arrisku-faktoreak ikertu zituen aldagai anitzeko eredua, leukopenia baino ez zuen adierazi esanguratsua estatistikoki *(ikus table 4)*.

Sei pazienteren bilakaera ez zen ona izan (%5,1): denek izan zituzten konplikazio akutu larriak (%5,1), bik sekuela iraunkorrak izan zituzten eta beste bi hil egin ziren. Sei pazienteak 26 egunetik beherakoak ziren, triangeluaren arabera egonkor ez zeudenak, prokaltzitonina balio altuekin (4,7-100ng/ml balio tarteekin); horietatik leukopenia, lau pazientetan identifikatu zen (2.300-9.200 leukozito/mm^3 tartea).

Taulak artikulu originaletik izan dira berreskuratuak zuzenean.

Table 1. Epidemiologic and clinical features, management, and outcomes of infants with late-onset disease Group B *Streptococcus*.

	Late-onset disease (N=118)
Sex (males) - *n (%)*	68 (57.6)
Age – *days, median (IQR)*	28 (16-43)
Normal PAT upon arrival - *n (%)*	56 (47.5)
Reported symptoms – *n (%)*	
Fever	86 (72.9)
Fever without a source	29 (24,6)
Fever with other symptoms	57 (48.3)
Irritability	38 (32.2)
Somnolence, lethargy	20 (16.9)
Respiratory symptoms	13 (11.0)
Others[1]	16 (13.6)
Fever, time since onset – *hours, median, (IQR)*	2 (0-4)
Normal PE – *n (%)*	56 (47.5)
Discharge to home *n (%)*	3 (2.5)
Admission *n (%)*	
Ward	80 (67.8)
PICU	35 (29.7)
<u>Outcomes</u> *n (%)*	
Acute complications	6 (5.1)
Sequelae	2 (1.7)
Death	2 (1.7)

[1]*Digestive, local pain.* ***CI****, confidence interval;* ***IQR****, interquartile range;* ***PAT****, Pediatric Assessment Triangle;* ***PE****, physical examination;* ***PICU****, pediatric intensive care unit.*

Table 2. Epidemiologic features, clinical characteristics, laboratory test results, and management with severe and non-severe infections.

	Non-severe infection[1] (n=44)	Severe infection[2] (n=74)	p-value
Sex (Males) - *n (%, 95% CI)*	28 (63.6, 47.8-77.6)	40 (54.1, 42.1-65.7)	n.s.
Risk factors for GBS - *n (%, 95% CI)*	3 (6.8, 1.4-18.7)	14 (18.9, 10.7-29.7)	n.s.
Age – *median days (IQR)*	28.5 (16-42.5)	28 (15-43)	n.s.
Normal PAT upon arrival - *n (%, 95% CI)*	41 (93.2, 81.3-98.6)	15 (20.3, 11.8-31.2)	**<0.001**
Normal PE upon arrival – *n (%, 95% CI)*	31 (70.5, 54.8-83.2)	25 (33.8, 23.2-45.7)	**<0.001**
Admission Ward PICU	 37 (84.1, 69.9-93.4) 4 (9.1, 2.5-21.7)	 43 (58.1, 46.1-69.5) 31 (41.9, 30.5-53.9)	**<0.001**
WBC – *(median /mm^3, IQR)* **- sensitivity (WBC <5,000 or >15,000/mcL)**	11,840 (8,300-16,455) 38.6% (95 % CI; 24.4-54.5%)	7,300 (4,100-11,200) 35.1% (95% CI: 24.4-47.1%)	**<0.001**
ANC - *(median /mm^3, IQR)* **- sensitivity (ANC <1,500 or >10,000/mcL)**	6,310 (4,500-10,598) 34.1% (95% CI: 20.5-49.9%)	4,530 (1,975-8,300) 35.1% (95% CI: 24.2-47.1%)	**0.01**
CRP – *(median mg/L, IQR)* **- sensitivity (CRP ≥20 mg/L)**	5.5 (2.1-18.0) 23.3% (95% CI: 11.8-38.6%)	7.7 (3.6-24.0) 29.7% (95% CI: 19.7-41.5%)	n.s.
PCT – *(median ng/ml, IQR)* **- sensitivity (PCT ≥0.5 ng/ml)**	1.7 (0.4-6.5) 71.8% (95% CI: 55.1-85.0%)	3.5 (0.7-21.8) 87.0% (95% CI: 75.1-94.6%)	n.s.

[1]Included: occult bacteremia and focal infection (osteoarticular and urinary tract infection); [2]Included: sepsis/septic shock, meningitis, and sepsis/septic shock with associated meningitis; ***CI****: confidence interval;* ***GBS****, Group B Streptococcus;* ***PAT****, Pediatric Assessment Triangle:* ***PE****, physical examination;* ***WBC****, white blood cell count;* ***ANC****, absolute neutrophil count;* ***CRP****, C-reactive protein;* ***PCT****, procalcitonin;* ***n.s.****, not significant.*

Table 3. Multivariate analysis to identify independent risk factors for severe infection.

Risk factors for severe infection	OR	95% CI	p-value
Age (days)	0.9	0.95-1.02	n.s.
Maximum temperature (ºC)	0.7	0.4-1.2	n.s.
Altered PAT upon arrival (%)	43.6	8.1-235.7	**<0.001**
Altered PE upon arrival (%)	1.5	0.3-6.9	n.s.
WBC – (/mm^3)			
Group 1: <5,000	1.5	0.05-45.3	n.s.
Group 2: 5,000-15,000	Reference	Reference	
Group 3: >15,000	5.1	0.6-45.4	n.s.
ANC – (/mm^3)			
Group 1: <1,500	1.2	0.02-86.1	n.s.
Group 2: 1,500-10,000	Reference	Reference	
Group 3: >10,000	0.2	0.02-2.3	n.s.
CRP – (mg/L)	1.0	0.9-1.0	n.s.
PCT – (ng/ml)	1.0	0.9-1.1	n.s.

***PAT**, Pediatric Assessment Triangle; **PE**, physical examination; **WBC**, white blood cell count; **ANC**, absolute neutrophil count; **CRP**, C-reactive protein; **PCT**, procalcitonin; **OR**, odds ratio; **CI**, confidence interval; **n.s.**, not significant.*

Table 4. Multivariate analysis to identify independent risk factors for pediatric intensive care unit admission.

Risk factors for PICU admission	OR	95% CI	p-value
Age (days)	0.9	0.9-1.0	n.s.
Maximum temperature (ºC)	1.0	0.3-3.9	n.s.
GBS infection risk factors (%)	1.4	0.3-6.7	n.s.
Altered PAT upon arrival (%)	7.1	0.9-56-5	n.s.
Altered PE upon arrival (%)	3.2	0.5-21.3	n.s.
WBC – (/mm^3)			
Group 1: <5,000	11.6	1.5-91.4	**0.019**
Group 2: 5,000-15,000	Reference	Reference	
Group 3: >15,000	0.08	0.01-2.2	n.s.
ANC – (/mm^3)			
Group 1: <1,500	0.8	0.1-8.1	n.s.
Group 2: 1,500-10,000	Reference	Reference	
Group 3: >10,000	7.0	0.3-156.7	n.s.
CRP – (mg/L)	1.1	0.999-1.14	n.s.
PCT – (ng/ml)	1.0	0.968-1.04	n.s.

***GBS**, Group B Streptococcus; **PAT**, Pediatric Assessment Triangle; **PE**, physical examination; **WBC**, white blood cell count; **ANC**, absolute neutrophil count; **CRP**, C-reactive protein; **PCT**, procalcitonin; **OR**, odds ratio; **CI**, confidence interval; **n.s.**, not significant.*

Bigarren mailako helburuaren araberako emaitza. Aurretiaz espero ez zen pandemiak larrialdi zerbitzu baten identifikatu diren IBIen epidemiologian izan duen eragina deskribatu

- Martin-Irazabal G, Gangoiti I, Gomez B, Lizarraga L, Mintegi S. Impact of the COVID-19 pandemic on pediatric invasive bacterial infections. An Pediatr (Engl Ed). 2023 Mar;98(3):228-229. doi: 10.1016/j.anpede.2023.01.013. Epub 2023 Feb 20. PMID: 36813615; PMCID: PMC9940794.

Azterketa-aldiak iraun zuen bi denbora tarteetan, 14 urtetik beherako pazienteei dagozkien 269.105 kontsulta erregistratu ziren larrialdi-zerbitzu pediatrikoan (153.736 aurrepandemian, 4.270 kontsulta/hilean, eta 115.369 pandemian, 3.393 kontsulta/hilean; diferentzia %20,5) eta aurrez osasuntsu ziren 119 pazientetan IBIa diagnostikatu zen. Pandemia aurreko aldian, 70 IBI diagnostikatu ziren eta 49 pandemian. Pandemia garaian, aurretiaz osasuntsu zen paziente baten IBI diagnostikatzeko probabilitatea nabarmen aldatu zen: handiena 2020an izan zen; 2021ean, neurri ez hain murriztaileekin eta kontsulten gorakadarekin hilabeteko IBI kopurua pandemia aurrekoa baino txikiagoa izan zen, eta aurrez osasuntsu zen pazientea IBI batekin diagnostikatzeko probabilitatea ere bai. Bi mila eta hogeitabigarren urtean, pandemia aurreko antzeko egoera irudikatu zen. Bestetik, pandemia garaiko IBIen erantzuleei dagokienez, aldaketa nabarmenak izan ziren; 2021ean *N. meningitidis* desagertu egin zen eta 2022an aldiz, *S. pneumoniae*ren hazkunde (9/22; diagnostikaturiko IBIen %40,9) handia eman zen. Hiru hilabetetik beherako haurrengan, B taldeko estreptokokoa izan zen IBIaren kausa nagusia pandemian (%33,3) vs. *E. coli* (%50) aurrepandemian $p<0,01$ (ikus Tabla 1).

Taulak artikulu originaletik izan dira berreskuratuak zuzenenan.

Tabla 1. Episodios totales e infecciones bacterianas invasivas (IBI) registradas en el servicio de urgencias pediátrico (SUP) antes y durante la pandemia por coronavirus SARS-CoV-2.

	Episodios en SUP	Episodios/ mes	IBI	IBI/mes	IBI/episodios	Bacterias más prevalentes
PRE-PANDEMIA	153.736	4.270	70	1,94	**1 IBI / 2196 episodios**	*S. pneumoniae* (18,6%) *N. meningitidis* (18,6%) *S. aureus* (17,1%) *E. coli* (15,7%) *S. agalactiae* (5,7%)
PANDEMIA						
2020	21.746	2.175	19	1,90	**1 IBI / 1144 episodios ***	*S. pneumoniae* (28,6%) *S. aureus* (20,4%) *N. meningitidis* (10%) *S. agalactiae* (10%) *E. coli* (10%)
2021	39.880	3.323	8	0,67 *	**1 IBI / 4985 episodios ***	
2022	53.743	4.478	22	1,83	**1 IBI / 2443 episodios**	

** p<0.01, al comparar con el periodo pre-pandemia.*

EZTABAIDA

Akatsetatik, gehiago entzuten, iraganetik, orainetik, etorkizunetik, zugandik, nigandik, guregandik, IKASTEN (Btx)

EZTABAIDA

Tesi honetan bildutako artikulu guztiek azpimarratu baino ez dute egiten hipotesian agertzen ziren ideien garrantzia. IBIen inguruan egin beharreko ikerkuntza eta zaintza jarraia ezinbesteko jarduera iruditzen zaigu larrialdi zerbitzu baten ager daitezkeen paziente hauen karakterizazioa egiteko, zein baldintzetan heltzen diren jakiteko, anamnesi, azterketa fisiko zein proba osagarriei atera lekieken etekina zein izan daitekeen jakiteko, IBIen bilakaera aurreikusteko eta bilakaera ilunenekin harremana izan ditzaketen arrisku faktoreak zein izan daitezkeen identifikatzeko. IBI bat paira dezakeen ume eta nerabeari eskaini dakiokeen kalitatezko arreta, bestelakoen artean, aurrez esan dugun guztiaren baitan egongo da. Azken batean, gure gizartean bizi izandako osasun nahiz gizarte arloko aldaketek, infekzio larrien behaketa sistemak eratzearen eta, existitzen diren kasuetan, indartzearen, garrantzia uzten dute agerian. Nahiz eta tesiaren muinean ez egon, COVIDak gure inguruan diagnostikatu diren IBIetan izan duen eraginak aurreko guztia baino ez du berresten.

Tesi honetan bildu diren ikerketa lanek erakusten duten ebidentzia nabarmenetakoa, IBIa pediatriako larrialdi zerbitzu baten artatzen diren kontsulten artean ez ohiko aurkikuntza dela da (%0,04-0,05eko tasa, hau da, larrialdi pediatriko zerbitzu batera datozen 2.500 umeetatik bat, gutxi gora-behera) eta hein handi baten aurrez osasuntsu diren pazienteetan agertzen direla. Irisgarritasun unibertsala duen osasun sistema baten dihardugula ulertuta, hain kasu bakan baina larriak ahalik ongien identifikatzea erronka handia da. Gainera, kontuan hartu behar da IBI mota askoren kasuak nabarmen gutxitu direla, txertaketa kanpainei esker batik bat beste arrazoi batzuen artean. Jaitsiera honek berak, medikuek IBIen aurrean bizi izan duten esposizioa gutxitu egin du, diagnosia zailduz.

Egia da IBI bat pairatu duten paziente pediatrikoen bilakaera, orokorrean, ona dela, baina heriotza eta iraunkorrak diren sekuela larriak ez dira hain arrotzak paziente hauetan. IBIa pairatu duten umeen karakterizazioa egitea helburu zuen artikuluan azaltzen da ebaluazio pediatrikorako triangelu egonkorra ez zuten pazienteek, sukarraz gain, sintoma agerikoak zituztenek eta sukarra hasi eta lehen 24 orduen azpitik artatuak zirenek, bilakaera okerragoa izan zutela. Hala ere, paziente horien ezaugarri klinikoak, diagnostikoa eta bilakaera ezberdina izan zen isolatutako bakterio patogenoaren arabera. Ikerketa horretan isolatutako patogenorik ohikoena *S. pneumoniae* izan zen, batik bat bakteriemia ezkutu eta pneumonia inbaditzailearen kausa nagusia eta, *N. meningitidis*ekin batera, shock eta meningitisaren kausa nagusia. IBI neumokozikoen artean bakteriemia ezkutu eta meningitisa maizago identifikatu ziren bi urtetik beherako umeengan eta neumonia nagusiagoengan. *S. pneumoniae*k eragindako heriotzak eta sekuela iraunkorrak artikulu honetan identifikatu ziren kasuen erdiak baino gehiago izan ziren. Prebentzio ekintza eta baliabideek, ondorioz, ezinbestekoak dirudite[194]. Egia da baita ere, isolatutako neumokokoen serotipoa ehuneko altu baten txerto antineumokoziko hamahirubalentearen babesaren barne legokeela, aurretiaz publikatua izan den moduan[197]. Gainera, *S. pneumoniae*ren prebalentzia globala gutxitu egin zen PCV13 ezarri ondoren; pentsatzen zen beherakada hori handiagoa zatekeela populazioren neumokokoarekiko txertaketa estaldura erabatekoa izan balitz[137]. Hala ere, serotipoen ordezkapena PCV7arekin baino azkarrago ematen ari zela esaten zuten adituak gero eta gehiago dira, batik bat 8 serotipoaren gehitzearekin[198]. Bestetik, azken urteetan ikusi da nola PCV13aren babespean behar lukeen 3 serotipoa, gaur egungo infekzio neumokoziko inbasiboen bigarren eragile nagusia dela[198], babes hori gainditzeko gaitasuna hartu duen kezka nagusitu egin delarik[199]. Merkaturatu diren edo egingo diren txerto antineumokoziko berriek babes hori emango dutela uste da. Dena den, eta sarreran aipatu dugunez, honen

inguruko informazioa aldatuz doa[200], ikerkuntza eta behaketa sistemek duten garrantzia azpimarratuz.

*N. meningitidis*a sepsiaren kausa nagusia izan zen eta beste IBIekin konparatuta larritasun handiagoarekin erlazionatu zen, aurretiaz publikatua izan den bezala[46]. Hala ere, artikulu honen berezitasunetako bat urte bitik gorakoen artean eman ziren infekzio meningokozikoen tasa izan zen, jakina delako urte betetik beherako haurren artean gertatzen dela meningokokoaren intzidentziarik handiena[201]. Beste serie batzuetan ez bezala[202,203], pazienteen ehuneko esanguratsu batek ez zuen azaleko rashik garatu, batez ere meningitis meningokozikoa diagnostikatu zen pazienteetan. Hau kontutan hartzekoa litzateke antibioterapia enpirikoaren aukeraketarik onena egiteko[204]. Orokorrean serie honetako infekzio meningokozikoa jasan zuten pazienteen eboluzioa, literaturan azaldutakoa[205] baino hobea da; agian gure pazienteen erupzio tasa ere neurri berean da baxuagoa, gure pazienteak larrialdietan beste zerbitzu batzuetan baino goizago artatzen direlako, beste arrazoi batzuen artean.

Aurretiaz ere publikatuta dago, *S. aureus* dela ume nagusietan gehien isolatzen den bakteria eta infekzio osteoartikular edo ehun bigunen infekzioekin erlazionatzen dela; sintomen iraupena ere luzeagoa izan ohi da eta gure seriea ere ez da salbuespena. Data basea osatu zenean eta batik bat artikulu honetarako analisia egin zenean, gaur egun kezkarako arrazoia den komunitaterekin erlazionatutako metizilinari erresistentea den *S. aureus*aren egoera ezagutzeko daturik ez zen bildu. Argi dagoena da, gure inguruan publikatu diren tasak[77] kezka arrazoi direla eta gure populazioaren prebalentzia kontuan hartu beharko dela antibiotiko egokiena hautatzeko orduan.

Odol-kulturen erregistro multizentrikotik eratorritako B taldeko estreptokokoak eragindako infekzio berantiarren analisian, atentzioa ematen du %5ak ondorio larriak izan

zituela eta heriotza tasa %2an ezarri zela. Infekzio larri bat garatzeko identifikatu zen arrisku faktore bakarra ebaluazio pediatrikorako triangeluan oinarritutako egonkortasun falta izan zen eta honek ondorio larriekin erlazioa izan zuela ematen du. Azpianalisi hau 7 eta 89 egun bitarteko haurren infekzio berantiarra inoiz aztertu duen serie prospektibo handienetako bat da eta *E. coli*ak eragindako bakteriemien inguruan argitaratutako datuekin alderatuta larriagoak direla ematen du, sepsia eta meningitisa maizago eragiten baititu[81] eta konplikazio akutu zein heriotzak ere ohikoagoak direlako.

*E. coli*a ikertu den azpianalisian ezberdindu ziren lau aurkezpenen artean, urtebetetik beherako haurren taldea eta batez ere, hiru hilabetetik beherakoena, gernu-infekzio inbaditzaileekin erlazionatu zela ikusi zen; eta egonkortasunik ez izatea, B taldeko estreptokokoak eragindako infekzioen modu berean, larritasun handiagoarekin. Horregatik da ezinbestekoa susmo-indize altua izatea paziente hauen aurrean gaudenean. Laburbilduz, haur gazteenek pairatzen dituzten infekzio bakterianoen ezaugarri ohikoak (bi bakterien kasuan) nahiko antzerakoak dira; oso goiz egiten dute kontsulta, zeinu eta sintomak normalean ez dira esanguratsuegiak eta egonkor daude. Horretan datza ebaluazio pediatrikorako triangeluaren balioa, batez ere egonkor ez daudenen artean, larritasun eta bilakaera ilunagoekin erlazionatuta.

Beste alde batetik, B taldeko estreptokokoa, odol-kulturan ez ezik beste medio batzuetan ere isolatu zen eta hein handi baten LZRan. Honek berretsi egiten du ziztada lunbarra egiteko gomendioa, jada aurretik egin ez bada, bakterio honen identifikazioa egiten bada 3 hilabetetik beherako haurren odol laginean[206].

Bestetik, *E. coli*ak eragindako gernu infekzioa duten 28 egunetik beherako haurrek dute bakteriemia pairatzeko arriskurik handiena[51]. Azken urteotan, ahaleginak egin dira bakteriemia izateko arrisku txikia duten balizko gernu-bideko infekzioarekin

diagnostikatu eta ospitaleratzerik gabeko maneiurako egokiak diren pazienteak identifikatzeko[207,208]. Izan ere hainbat ikerketetan esan da antibioterapia egokiarekin tratatu diren haur hauen bilakaera ona eta segurua izan dela, atxikitutako bakteriemia pairatu edo ez[209]. Hala ere, gure ikerketan meningitis bakterianoa zuten haur guztiak, bat izan ezik, bi hilabete baino gazteagoak ziren, eta *E. coli*ak eragindako bakteriemia zuten hilabetez azpiko umeen %10ak meningitisa pairatu zuen. Publikatua izan da gernu infekzioari lotutako meningitis arriskua hilabetetik beherako haurretan[210]. Gure ikerketak ziztada lunbarra egiteko gomendioa berresten du *E. coli*aren identifikazioa egin ezkero hilabete bat edo hilabetetik beherako haurraren odol-laginean. Aurrez osasuntsua ez izateak *E. coli*ak eragindako infekzio inbaditzailearen larritasuna areagotu zuen gure ikerketan, baina batik bat, ebaluazio pediatrikorako triangeluaren arabera definitzen den egonkortasun faltak; ondorioz, ume hauekin egin beharreko maneiua kontu handiz egin beharrekoa izango da.

Tesiari hasiera ematen dion ikerketan, deigarria egin zitzaigun emaitza kezkagarri batez jabetu ginen: diagnostikoa egin aurretik, larrialdietara beste bisitaren bat egin zuten pazienteen kopurua. Ehuneko hori aurretik jakinarazitakoa baino zerbait txikiagoa izan zen arren[24], bigarren bisitan diagnostikatu ziren pazienteen hilkortasun-tasa eta sekuelen proportzioa handiagoak izan ziren, nahiz eta estadistikoki ez izan esanguratsua. Iradoki da sukarra eta itxura ona duen haurraren sepsi edo meningitiserako progresioa aurrez igarri ezin den zerbait dela eta, ondorioz, lehen bisitan egiten den ebaluazio kliniko sakon estandarizatuak nahikoa izan beharko lukeela[25]. Hala ere, lehen aurkikuntza haiek eta gerora tesiaren parte den “larrialdi zerbitzuan errepikatzen diren bisiten” ikerketa espezifikoan agertzen direnek, larrialdi zerbitzuan egindako artatzea eta gerora, lehen mailako arretako mediku baten jarraipen zorrotzaren beharra iradoki zuten, gurasoek etxean egin behar zituzten zaintza lanen gomendioak argi azaltzeaz gain.

Vaillancourt et al.en artikuluak adierazi zuen azkenik sepsia garatu zuen pazientearen azken bilakaera ez zela ezberdina izan ingresatu aurreko bisita bakarra edo gehiago izan zituztenen artean. Lehen bisitan, sepsia eta meningitisa berez ez zeudela argudiatu zen editorial baten, eta ondorioz, diagnostikoa egitea ezinezkoa zela[25]. Argi dago baieztapen hau eztabaidagarria dela. IBIak dituzten pazienteen kudeaketari buruzko gomendioek, eta zehazki sepsiaren kasuan, azpimarratzen dute infekzio posiblea adierazten duten zeinu edo sintomak dituzten pazienteengan sepsia goiz identifikatzearen garrantzia; antibiotikoen administrazioa atzeratzeak sepsiaren eta meningitisaren bilakaeran eragina du[41].

Pentsa daiteke kontsulta oso goiztiar baten egiten den azterketa fisikoaren errendimendua agian ez dela onena. Gure seriean lehen bisitan diagnostikatu ez ziren pazienteen bi herenetan ez zen proba osagarririk egin. Esana dago sepsiaren behaketa egiteko tresna edo baliabide bateria baten beharra egon badagoela, baina eraginkorrak izan daitezen, larrialdi zerbitzu batera datozen paziente guztietan egin beharrekoak lirateke. Egia esan, tresna gehienek parametro klinikoak erabiltzea azpimarratzen dute laborategiko probak egin beharrean[211]. Hala ere, sukarra dela eta kontsultatzen duten paziente askok, sepsia paira dezaketen abisu seinaleak dituzte, nahiz eta berez osatzen diren infekzioak izan seinale horien erantzule gehienetan. Guzti hau martxan jartzeak, errekurtso, neke eta iatrogeniaren gorakada argia dakarrela jakin badaki komunitate zientifikoak[212]. Eta alderantziz, paziente pediatrikoa sarritan gai izaten da sepsiaren hasierako faseetan parametro hemodinamiko normalak mantentzeko.

Hori dela eta, behin sepsi abisua eman duen pazientearengan proba osagarriak egitea zilegi da, baita maneiu protokolo zehaztuek gomendatzen dituzten pazienteetan ere.

Proba osagarri hauen artean larrialdi zerbitzu baten erabiltzen diren odol-analisi ohikoen laguntzaz, IBIa izateko arriskua duten pazientearen profila zehazten saiatu ginen.

Izan ere, mikrobiologikoki baieztatutako IBIa izan zuten aurrez osasuntsu ziren paziente gehienek, ohikoenak diren odol analisietako baten alterazioa erakutsi zuten gutxienez. Azaldu dugu, hala ere, markatzaile horien sentsibilitatea aldatu egin zela isolatutako bakterio eragilearen eta pazienteak jaso zuen azken diagnostikoaren arabera. Orokorrean, prokaltzitonina eta C proteina erreaktiboa beste markatzaile klasikoak baino gehiagotan areagotu ziren, batez ere sepsia edo meningitisa bezalako gaixotasun larria zuten pazienteengan, baina haien sentsibilitatea eskasa izan zen bakteriemia ezkutua zutenengan.

Prokaltzitoninak bere aldetik abantaila batzuk eskaintzen ditu IBI[99], duten pazienteak identifikatzeko, meningitisa[130] eta baita infekzio meningokoziko[205] inbasiboa ere. Badirudi, C proteina erreaktiboa erabilgarriagoa dela infekzio fokal inbaditzailea izan dezakeen pazientea ebaluatzen denean, batez ere *Staphylococcus aureus*ek eragindako ehun bigunen infekzio eta infekzio osteoartikularretan. B taldeko estreptokokoaren kasuan leukopenia izan zen zainketa berezien unitatean ingresatzeko arrisku faktore bakarra, baina ez zen izan ondorio larriak izateko arrisku faktore, aurretik esan izan den moduan[213,214].

Bakteriemia ezkutua duten haurrek arreta berezia merezi dute. Egonkor daude eta fokorik gabeko sukarra baino ez dute adierazten paziente hauek. Gure seriean prokaltzitoninak ez du oso errentagarria ematen bakteriemia ezkutu neumokozikoaren kasuan, lehenago C proteina erreaktiboaren errendimendua jakinarazi zen moduan[18]. Ematen du markatzaile klasikoak baliagarriago liratekeela, eta horien artean leukozitoen zenbaketa. Lehenago esan dugun moduan, paziente hauek ebaluatzerako orduan odol analisiak indikazio gabe egiteak edota markatzaile gehiago eskatzeak, antibiotikoen ezarpen eta beharrezko ez diren maneiuak jasotzen dituzten pazienteen kopurua handitu dezakete, jaso beharko

lituzkeen taldea hobeto identifikatu beharrean[19]. Hala ere, testa egiteak gomendagarria dirudi sukar oso altua duen bularreko haurraren kasuan.

Eztabaidan ezin ahaztu azken urteotan bizi izan dugun pandemiak nolako bizi, jarrera, ohitura eta osasun aldaketak eragin dituen eta etorkizunean etor daitezkeen berrietarako ikasketa izan beharko lukeela.

Pandemia garaian, larrialdietan artatua izan zen paziente osasuntsu batek IBI bat izateko probabilitatea asko aldatu zen. Hala ere, pandemiaren bigarren urtean IBI diagnostikatu zitzaien pazienteen kopuru absolutuaren beherakada horren azalpenik ez dugu aurkitu. Garrantzitsutzat jotzen dugu paziente horiek artatzen dituzten medikuek informazio hori ezagutzea; izan ere, oker pentsa liteke, arnas bidezko kutsagarritasuna txikiagoa izanda, larrialdietan artatzen den paziente bati IBIa diagnostikatzeko aukera txikiagoa dela. Gainera, IBIaren prebalentziaren aldaketak eragina izan dezake iragarpen klinikoa burutzen duten "score" desberdinetan edo IBIa duten pazienteak identifikatzeko gehien erabiltzen diren tresna eta baliabideen errendimenduan. Babes-neurriak zorrotzenak izan zirenean, ia infekzio meningokoziko inbasibo orokorraren erabateko desagertzea etorri zen: Espainian 0,14 kasu 100.000 biztanleko intzidentzia tasaraino[67] jaitsi zen eta antzeko egoerak bizi izan ziren beste herrialde batzuetan ere[68,215]. Gerora, pandemian hartutako neurrien erlaxazioaren ondorioz, gaixotasun meningokozikoaren areagotzea adierazten duten datuak publikatu dituzte zenbait herrialdek, Erresuma Batuak kasu[216]. Bestetik, 2022an infekzio inbaditzaile neumokozikoen berragertze nabarmena ikusi zen, diagnostikaturiko IBIen %40,9ra iritsi zena gure seriean. Bai pandemiak eragin dituen eta bai berez IBIek pairatzen dituzten intzidentzia uhinek, IBIen zaintza sistema sendoak diseinatzeko beharra indartzen dute.

Tesi honetan bildu diren artikuluek, guztiek, dituzte berezko mugak.

Tesiaren oinarri den erregistroak, unizentrikoa izaki, emaitzak estrapolatzeko orduan kontu handia izatea eskatzen du. Artikuluak ondorengoak dira: “Characteristics of children with microbiologically confirmed invasive bacterial infections in the emergency department”; “Markers for invasive bacterial infections in previously healthy children”; “Repeated Emergency Department Visits Among Children with Invasive Bacterial Infections”; “Impact of the COVID-19 pandemic on pediatric invasive bacterial infections”.

Hala ere, antzeko ezaugarriak biltzen dituzten populazioetan erabilgarri izan daitezke. Ikerketa erretrospektiboa izanda, data galeraren bat egon izan zitekeen. Hala ere, aurrera begira burututako erregistro batean oinarritzen da. Honen eskuragarritasuna, larrialdizerbitzu pediatrikoaren historia elektronikotik dator, osasun sistema publikoak gaitutako data-base elektronikoan oinarrituta. Ikertutako laginaren tamaina beti izan daiteke handiagoa, baina urtez urte handitzen joan den lagina da eta erregistroak zabalik jarraitzen du egun. Odolean edo likido zefalorrakideoan bakteriarik isolatu ez zitzaizkien pazienteak ez ziren ikerketan sartu eta ondorioz, odol analisi desberdinen espezifikotasuna eta balio prediktiboak ezin izan dira zehaztu, baina sentikortasunaren balioa garrantzitsua deritzogu paziente hauek artatzeko momentuan.

Bakteriemiaren prebalentzia kalkulatzea helburu zuen artikulu unizentrikoaren mugak antzekoak dira, baina prospektiboki bildu diren datuak izaki, ez dugu pazienterik galdu zenik uste (“Prevalence of Occult Bacteremia in Infants With Very High Fever Without a Source”). Zentruanitzaren kasuan, laginaren tamaina da muga nagusia (“Occult bacteremia in young children with very high fever without a source: a multicenter study”). Egia da hasierako helburua 500-1.000 paziente biltzekoa zela, baina ikerketa 200 pazientera iritsi zenean eta bakteriemia tasa %3 zela ohartuta, emaitzak argitaratzea

lehenetsi genuen ez baikenuen uste etikoa zenik ikerkuntzarekin jarraitzea emaitzak komunikatu gabe. Gisa horretan onartu zuen aldizkari zientifikoak.

Hirugarrenik, gure erregistroa ez zen diseinatu *E. coli* edo B taldeko estreptokokoaren larritasun edo karakterizazioa egiteko baina bildutako datu eta emaitzek balioa ematen die lortutako ondorioei ("Paediatric *Escherichia coli* bacteraemia presentations and high-risk factors in the emergency department"; "Late-onset Group B *Streptococcus* Bacteremia Evaluated in the Pediatric Emergency Department and Risk Factors for Severe Infection"). Egia da, *E. coli*ak eragindako gernu-infekzio inbaditzaileak hein handi baten aztertu ditugula artikulu baten, jakin arren ez dela gernu-infekzioak eragiten dituen mikroorganismo bakarra. Beraz, emaitzak ezin dira gernu-infekzio inbaditzaile guztietara zabaldu. Gainera, gernu-infekziorik gabeko *E. coli*ak eragindako bakteriemiak aztertu dugu artikuluan. Likido zefalorrakideoaren azterketari dagokionean, nahiz eta ikerketa gehiago eta handiagoak agian beharrezkoak izan, gure datuek bi hilabetez azpiko haurretan ziztada lunbarraren gomendioa babesten dute.

Azkenik, B taldeko estreptokokoaren azpi-ikerketan ez ziren arrisku faktore guztiak kontutan hartu; pazienteak zainketa berezien unitatean sartzeko irizpideak agian ez ziren homogeneoak izan, ezta agian arnas-euskarri edo euskarri hemodinamikoari ekiteko irizpideak eurak ere. Hala ere, bildutako datuek B taldeko estreptokokoaren karakterizazioa egiteko aukera ematen digutela uste dugu. Are gehiago, gure ikerketak (arrisku faktoreak B taldeko estreptokokoaren bakteriemia berantiarren %20ak baino gutxiagok zituzten) erditze barruko antibioterapiak bakteriemia berantiarrarengan duen eragina, goiztiarrarengan daukana baino askoz ahulagoa den ideia indartzen du eta beste neurri batzuen beharra irudikatu, haurdun dauden emakumeengan ezarriko liratekeen txerto multibalenteena kasu.

ONDORIOAK

Galderak aldatuz bakarrik lortuko dugu gakoa datekeen erantzuna (Btx)

ONDORIOAK

Ikerkuntza lan honek gertatu diren osasun eta gizarte mailako aldaketak medio, IBI batek gure inguruko larrialdi zerbitzu pediatriko baten aurkez dezakeen irudi klinikoaren ezagutzan lagun dezake. Beste alde batetik hura identifikatzeko ditugun baliabide sortaren ezagutza handitzeko tresna izan daiteke.

Helburuen araberako ondorioak hurrenez hurren:

- **Hamalau urtetik beherako pazienteetan baieztatu diren IBIen aurkezpen klinikoaren karakterizazioa egin eta haien larritasuna deskribatu**.

Characteristics of children with microbiologically confirmed invasive bacterial infections in the emergency department. EJEM 2018.

  - Gaur egungo IBI pediatrikoen karakterizazioan pazientearen adin eta isolatutako bakterio patogenoak indar handia du. Aurrez osasuntsu diren paziente gazteak dira gehien pairatzen dituztenak.
  - Infekzio inbaditzailea duten pazientearen bilakaera, oro har, ona da. Prozesu larriagoekin erlazionatzen dira larrialdi zerbitzura egonkor iristen ez diren pazienteak, sukarraz gain beste sintomaren bat atxikituta dutenak eta prozesuaren iraupen laburra dutenak.
  - *S. pneumoniae* izan da kopuruz heriotza eta sekuela larri gehienen arduraduna, *N. meningitidis*aren aurretik.

Repeated Emergency Department Visits Among Children with Invasive Bacterial Infections. PIDJ 2021.

  - IBI duten pazienteak larrialdi zerbitzu baten artatu diren lehen kontsultan egoki ez identifikatzea eta ondoriozko antibioterapia ez ezartzea ondorio

larriagoekin dago erlazionatuta. Ahalik eta maneiu egokienak diseinatu behar dira IBIen identifikazio goiztiarra egiteko.

- **Hamalau urtetik beherako pazienteen IBIak identifikatzeko egiten diren ohiko odol-testen (leukozitoen zenbaketa, neutrofiloen zenbaki absolutua, proteina C erreaktiboa eta prokaltzitonina) balioa analizatu.**

Markers for invasive bacterial infections in previously healthy children. Am J Emerg Med. 2021.

  - IBIa duten pazienteek larrialdi zerbitzu baten ebaluatuak izatean, egiten zaizkien odol-markatzaile ohikoenen alterazioak izaten dituzte. Markatzaile hauen sentikortasuna aldatu egiten da bakteria eragile eta azken diagnosiaren arabera.

- **Fokurik gabeko sukarra duten eta larrialdi zerbitzura egonkor iristen diren 3-24 hilabete arteko haurrak artatzerakoan odol-testik ez erabiltzearen gomendioa ebaluatu.**

Prevalence of Occult Bacteremia in Infants With Very High Fever Without a Source. PIDJ 2018.

  - Baliteke egonkor dauden eta sukarra duten bularreko haurretan bakteriemiaren bilaketarako testik ez egiteko gomendioa berraztertu behar izatea fokurik gabeko 40,5ºC-ko sukarra edo gehiago duten pazienteetan.

Occult Bacteremia in Young Children with Very High Fever Without a Source: A Multicenter Study. PIDJ 2020.

  - Egonkor dauden eta jatorri argirik gabeko sukarra duten 3-24 hilabete arteko pazienteengan bakteriemia ezkutuaren baheketa egiteko

gomendiorik egon ez arren, litekeena litzateke gomendio hauen berrazterketa egin beharra jatorri argirik gabeko sukarraren tenperatura 40,5ºC edo handiagoa denean, txertaketa egoera edozein delarik ere.

- ***E. coli*k eragindako infekzio inbaditzaileen aurkezpena deskribatu eta balizko profilak eta larritasunarekiko balizko harremana ikertu.**

Paediatric *Escherichia coli* bacteraemia presentations and high-risk factors in the emergency department. Acta Paediatr 2021.

  - Larrialdi zerbitzu pediatriko baten artatzen diren *E. coli*ak eragindako bakteriemiak lau aurkezpen mota irudikatu ditu eta bakoitzaren larritasun-tasa desberdina da. Gernu-infekzioarekin erlazionatutako bakteriemia egonkor zeuden 12 hilabetetik beherako haurrengan izan zen sarriena eta bilakaera onarekin erlazionatu zen. Adinez zaharragoek, egonkor iristen ez zirenek eta aurrez osasuntsu ez zirenen bilakaera okerragoa izan zen. Bi hilabete baino gehiagoko pazienteek *E. coli*ak eragindako meningitisa pairatzea ezohikoa da.

- **B taldeko estreptokokoak eragindako infekzio inbaditzailearen aurkezpena deskribatu eta haren larritasunarekiko balizko harremana ikertu.**

Late-onset Group B *Streptococcus* Bacteremia Evaluated in the Pediatric Emergency Department and Risk Factors for Severe Infection. PIDJ 2022.

  - B taldeko estreptokokoaren ondoriozko bakteriemia berantiarra duten haurrek maiz garatzen dituzte sepsia eta meningitisa; hilkortasun eta erikortasun tasa ez dira arbuiagarriak, batez ere ebaluazio pediatrikorako triangelu egonkorra ez duten eta leukopenia pairatzen dutenengan. Prebentzio estrategia desberdinak behar dira.

- **Bigarren mailako helburua. Aurretik espero ez genuen pandemia batek larrialdi-zerbitzu baten identifikatu diren IBIen epidemiologian izan duen eragina deskribatu.**

Impact of the COVID-19 pandemic on pediatric invasive bacterial infections. An Pediatr (Engl Ed). 2023.

  - Pandemia garaian IBIaren prebalentziak jasan dituen gora beheren harira, IBIen bilakaera kontrolatzen duten zaintza-sistema sendoak diseinatzeko beharra dago osasun sistema osatzen duten profesionalak prest egon daitezen antzeko egoera berri bati aurre egiteko.

ETORKIZUNA

Etorkizuna ginenean, erreza zirudien denak (Leihotikan)

Galdera handiegia agian, erantzun sinple baterako (Kerobia)

ETORKIZUNA

Eta, etorkizunean zer? Erronka handia da. Historiak hainbeste alditan erakutsi digu zer nolako garrantzia duen ikerkuntzak. Azken hamarkadetan hainbeste aldatu den mundu honetan, ikerkuntza erabat beharrezkoa zaigu aldaketa sozialek familia batek ume bat larrialdi zerbitzura eraman edo ez hartzeko erabakian zenbaterainoko eragina izan duten ulertzeko; paziente baten IBIa izateko duen arriskuak mediku eta sistemarengan duen eragina ulertzeko; edo, zergatik ez, teknologia berrien laguntzaz larrialdi zerbitzura hurbildu zaigun haurraren IBIaren identifikazioa erraztuko diguten tresna berriak ezagutzeko.

Giltzarriak arlo askotan egongo diren arren, nik lau aipatuko nituzke tesi honetan.

- Prebentzio neurriak ezinbestekoak dira. Eztabaidan hitz egindakoaren eta batik bat pandemia garaian bizi eta frogatuta geratu zen moduan txertaketa programen ezarpena mugarri da. Gaixotasun neumokoziko eta meningokozikoaren inguruan Espainiako Pediatria Elkartearen baitan dagoen Txertaketen Aholkularitza Batzordeak argi ditu ezarpenak. Merkaturatu eta merkaturatuko diren txerto konjokatu multibalente ezberdinen inguruan esperantza ugari dago, baita haurdun dauden emakumeengan proposatu diren B taldeko estreptokokoaren kontrakoan ere.
- Gaixotasun infekziosoen identifikazioa erraztu eta azkartu dituzten teknika berriak. Aurretik erabiltitako hazkuntza sistemak, gaur egun, teknika berriekin konbinatzen dira. Azken urteetan hainbat aurrerapauso eman dira identifikazio tekniken baitan eta horien artean daude PCRan oinarritzen direnak. Teknika estandarra, material genetikoa (DNA edo RNA) anplifikatzean oinarritzen da; kopia ugari sortzen ditu, ondoren immunofluoreszentzia bidez kontabilizatzen

direnak[217]. Teknika honek prozesu patologiko ugari diagnostikatzeko aukera ematen du eta egun, odol, likido zefalorrakideo, likido pleural, arnas-bideetako jariakin eta abarretan egiten da. Teknika berriek hainbat pausu murriztea ahalbidetu dute eta emaitzak oso denbora laburrean izatea. Hala ere, teknika hauek, gainontzeko froga osagarrien modura maneiu terapeutiko zehatzen barruan egitea gomendatzen dira, positibo faltsuak eta behar ez diren tratamendu eta ekintzak ekidin asmoz.

- Tratamenduak. Antibiotikoekiko erresistentzien igoera kezka iturri nabarmena da. Espektro murrizketak, indikazio egokiak… ezinbestekoak izango dira IBIen kontrola lortzeko antibiotikoen bateria eskuragarri izan nahi badugu.
- Pandemiak, baina baita pandemia aurreko egoerak ere, erakutsi du noraino den ezinbesteko gaixotasun infekziosoen bilakaera kontrolatzen duten sistema sendoak izatea. Hauek, IBI eta beste gaixotasunen monitorizazioa egiteaz gain, tokian tokiko eta momentuan momentuko erabakiak hartu eta ekintzak burutzeko aukera errazten baitute.

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TRADUCCIÓN AL CASTELLANO

IDENTIFICACIÓN DE INFECCIONES BACTERIANAS INVASIVAS EN PEDIATRÍA EN LA ERA DE LAS VACUNAS CONJUGADAS

Versión Castellano

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ÍNDICE ABREVIADO

ÍNDICE COMPLETO

ABREVIATURAS

ADN: ácido desoxirribonucleico.

ARN: ácido ribonucleico.

IBI: infección bacteriana invasiva.

IC: intervalo de confianza.

LCR: líquido cefalorraquídeo.

PCR: reacción en cadena de la polimerasa.

PCV7 y PCV13V: Vacuna conjugada antineumocócica heptavalente y trecevalente.

SAMR: *Staphylococcus aureus* resistente a la meticilina

SEUP: Sociedad española de Urgencias de Pediatría.

SIRS: síndrome de respuesta inflamatoria sistémica

SUP: Servicio de urgencias pediátrico.

TEP: Triangulo de evaluación pediátrica.

UCI: unidad de cuidados intensivos.

VIH: virus de la inmunodeficiencia humana.

RESUMEN

La fiebre es un motivo habitual de consulta entre los pacientes atendidos en un servicio pediátrico de urgencias. La causa más frecuente de la fiebre es una infección viral autolimitada, pero en ocasiones puede ser el primer síntoma de una infección bacteriana invasiva (IBI). El diagnóstico de IBI en un paciente se basa en el aislamiento de una bacteria patógena en sangre, líquido cefalorraquídeo, pleural o articular, siendo lo más preocupante el aislamiento en sangre y en líquido cefalorraquídeo.

El núcleo de esta tesis son ocho artículos publicados entre 2018 y 2023.

En la introducción se enumeran cada una de las bacterias más frecuentes que dan lugar a la mayoría de las IBI en la época pediátrica, con sus respectivas características y se describen uno a uno los diferentes cuadros clínicos que puede provocar cada IBI. En esta tesis, que ha partido de un servicio de urgencias pediátrico (SUP), también se describe el conjunto de herramientas que los pediatras que trabajan en él pueden utilizar para identificar un paciente con IBI. De hecho, la rentabilidad de la utilización de estas herramientas ha ido cambiando a lo largo de los años, como consecuencia principalmente de los cambios epidemiológicos y la disponibilidad de nuevos recursos.

Creemos que conocer la epidemiología y formas de presentación actuales de las IBIs en la población pediátrica y el rendimiento de los diferentes recursos utilizados para su manejo es crucial para establecer estrategias diagnósticas y de tratamiento que ayuden a identificar y tratar con mayor certeza y prontitud a estos pacientes.

La principal hipótesis de trabajo es que la caracterización del paciente que sufre una IBI y el rendimiento de los recursos disponibles para su identificación han sufrido cambios en los últimos años.

Los objetivos principales han sido caracterizar y describir la gravedad de las formas de presentación de las IBI confirmadas en pacientes menores de catorce años, entre ellas las producidas por *E. coli* y el estreptococo de grupo B. También se ha tratado de analizar el valor de los test de sangre convencionales utilizados para la identificación de IBI (recuento de leucocitos, número absoluto de neutrófilos, proteína C reactiva y procalcitonina) y la recomendación de no utilizar de manera sistemática test de sangre al evaluar a los niños de 3 a 24 meses previamente sanos que se presentan con fiebre sin foco y llegan estables al servicio de urgencias. Aunque no era un objetivo principal de esta tesis, también hemos querido describir el impacto de una pandemia no esperada sobre la epidemiología de las IBI identificadas en un servicio de urgencias.

Como se ha indicado anteriormente, para el desarrollo de esta tesis se han incluido ocho artículos.

Cuatro publicaciones son el resultado de un estudio de cohorte, basado en una base de datos registrada prospectivamente, abierta en 2008 en un servicio de urgencias pediátrico de un hospital terciario, donde se incluyeron pacientes menores de 14 años diagnosticados de una IBI.

En el artículo *Gangoiti I, Valle JR, Sota M, Martínez-Indart L, Benito J, Mintegi S. Characteristics of children with microbiologically confirmed invasive bacterial infections in the emergency department. Eur J Emerg Med. 2018 Aug; 25 (4) 274-280*, se analizaron los 223 pacientes diagnosticados de IBI durante un periodo de ocho años, de los cuales el 83,9% eran pacientes previamente sanos. Los casos de IBI debidos a neumococo y meningococo representaron casi la mitad del global. La edad de los pacientes, las características clínicas y el diagnóstico final variaron en función del microorganismo causante. Las infecciones meningocócicas fueron las IBI más graves. Aunque la mayoría

evolucionó bien, cuatro niños (1,8%) fallecieron y otros 8 (3,6%) sufrieron secuelas permanentes. La IBI se diagnosticó en una segunda visita en urgencias en 32 pacientes (14,3%), de los cuales, cuatro (12,5%) sufrieron muerte o secuelas permanentes. Se definieron factores de riesgo independientes para una mayor gravedad: haber sido atendidos en el servicio de urgencias en las primeras 24 horas de la enfermedad, la presencia de algún otro síntoma además de fiebre y la inestabilidad detectada mediante el triángulo de evaluación pediátrica (TEP) al llegar al servicio de urgencias.

El artículo *Gangoiti I, Gorostizaga Z, Aranzamendi M, Gomez B, Benito J, Mintegi S. Repeated Emergency Department Visits Among Children with Invasive Bacterial Infections. Pediatr Infect Dis J. 2021 May 1*; *40 (5)*, incluyó los pacientes diagnosticados de IBI durante 14 años, un total de 342, seleccionando para el análisis los 271 pacientes previamente sanos. Ciento noventa y nueve pacientes (73,4%) recibieron antibiótico parenteral en su primera visita. En 15 pacientes se objetivaron criterios de gravedad, y de ellos siete no habían recibido antibioterapia en la primera visita.

En el artículo *Gangoiti I, Fernandez CL, Gallego M, Gomez B, Benito J, Mintegi S. Markers for invasive bacterial infections in previously healthy children. Am J Emerg Med. 2021 Oct 48: 83-86* se incluyeron los pacientes diagnosticados de IBI durante trece años, un total de 367, pero el análisis se realizó con los 286 pacientes previamente sanos. Doscientos pacientes presentaron un TEP estable (69,9%) al llegar al servicio de urgencias. Los diagnósticos finales fueron sepsis 64 (22,4%), meningitis 38 (13,3%), bacteriemia oculta 63 (22,0%) e infección focal invasiva 121 (42,3%) (infección respiratoria 46, urinaria 33, infección osteoarticular o de tejidos blandos 33 y otros 9). Las bacterias aisladas más frecuentes fueron *Streptococcus pneumoniae* 89 (31,1%),

Neisseria meningitidis 61 (21,3%), *Escherichia coli* 40 (14%) y *Staphylococcus aureus* 36 (12,6%).

Globalmente, 265 (92,7%) tuvieron al menos un valor sanguíneo alterado. La sensibilidad de cada marcador sanguíneo varió en función del diagnóstico final y la bacteria causante. En el caso de sepsis y meningitis la sensibilidad de la procalcitonina y la proteína C reactiva fue mayor y en las infecciones focales invasivas el de la proteína C reactiva. En las infecciones provocadas por meningococo el biomarcador más sensible fue la procalcitonina y en el caso de *S. aureus* la proteína C reactiva. La sensibilidad de cada uno de los marcadores sanguíneos en los niños entre 3 y 24 meses que recibieron como diagnóstico bacteriemia oculta neumocócica fue del 43,5% para la procalcitonina (IC 95%: 25,6-63,2); de 48,3% para la proteína reactiva C reactiva (IC 95%: 31,4-65,6); del 75,9% para el recuento de leucocitos (IC 95%: 57,8-87,8) y del 58,6% para el número absoluto de neutrófilos (IC 95%: 40,7-74,5).

En el artículo de *Martín-Irazabal G, Gangoiti I, Gómez B, Lizarraga L, Mintegi S. Impact of the COVID-19 pandemic on pediatric invasive bacterial infections. An Pediatr (Engl Ed). 2023 Mar; 98 (3); 228-229* distinguimos dos periodos de tiempo, tomando como punto de corte la declaración de la pandemia. En el periodo prepandemia, se diagnosticaron 70 IBI y 49 durante la pandemia. Durante la pandemia, la probabilidad de diagnosticar IBI en un paciente previamente sano varió considerablemente. Por otro lado, en cuanto a las bacterias responsables de IBI durante la pandemia, se produjeron cambios significativos; desapareció la *N. meningitidis* en 2021, mientras que en 2022 se produjo un incremento importante de *S. pneumoniae* (9/22; 40,9% de las IBI diagnosticadas). En niños menores de tres meses, el estreptococo del grupo B fue la principal causa de IBI durante la pandemia (33,3%) vs. *E. coli* (50%) en prepandemia ($p < 0,01$).

Los artículos escritos con el objetivo de investigar la caracterización del estreptococo del grupo B y del *E. coli* y su posible relación con la gravedad, son el resultado del análisis secundario de un gran registro prospectivo que tenía como objetivo realizar la caracterización de las bacteriemias que se detectan en la edad pediátrica. En 2010, la Sociedad Española de Urgencias de Pediatría (SEUP), liderada por el Grupo de Trabajo de Enfermedades Infecciosas, propuso establecer un registro multicéntrico prospectivo de los cultivos sanguíneos positivos aislados en los servicios de urgencias de pediatría en España. El reclutamiento prospectivo de pacientes con edades comprendidas entre los niños recién nacidos y los 20 años se llevó a cabo entre 2011 y 2016. En 1.696 pacientes se aisló una bacteria patógena real en sangre. Para alcanzar los objetivos de estos estudios, se analizaron los pacientes en los que en su muestra de sangre se aislaron estreptococo del grupo B y *E. Coli*.

En el artículo de *Elgoibar B, Gangoiti I, García-García JJ, Hernández-Bou S, Gómez B, Martínez Indart L, Mintegi S; Bacteremia Study Working Group from the Infectious Diseases Working Group, Spanish Society of Pediatric Emergencies (SEUP). Paediatric Escherichia coli bacteraemia presentations and high-risk factors in the emergency department. Acta Paediatr. 2021 Mar; 110 (3);1032-1037* se identificaron 291 pacientes diagnosticados de IBI por *E. coli*. Los diagnósticos más frecuentes recogidos fueron la infección invasiva urinaria en 206 casos (70,8%), la sepsis 32 (11%) y la bacteriemia oculta 27 (9,3%). Cuarenta y tres casos cumplieron criterios de gravedad (14,8%, IC 95%: 11,2-19,3) y de ellos, dos fallecieron. Los análisis de Correspondencia Múltiple y en análisis Clúster identificaron cuatro tipos principales de presentaciones de la bacteriemia pediátrica por *E. coli*. Los dos primeros grupos fueron formados por niños previamente sanos menores de un año y con buen aspecto general, diagnosticados de IBI secundaria a infección urinaria y con una buena evolución en general. El tercer grupo estaba formado

en gran parte por pacientes previamente no sanos, de más de 12 meses de edad; en el último grupo había niños de diferentes edades, un tercio no era previamente sano y la proporción de niños inestables según el TEP era mayor que en el resto de grupos. Estos dos últimos grupos tenían menor relación infección urinaria y las tasas de gravedad fueron significativamente superiores, 15% y 50,9% respectivamente ($p < 0,01$). Los dos pacientes fallecidos pertenecían al último grupo. Ocho niños fueron diagnosticados de meningitis bacteriana, todos ellos menores de 5 meses. La tasa de meningitis detectada en las bacteriemias causadas por *E. coli* en lactantes menores de un mes de edad fue del 9,4% y en los niños de uno y dos meses 2,6%. Únicamente se diagnosticó un caso de meningitis en niños mayores de dos meses.

En el artículo de *Ecclesia FG, Alonso Cadenas JA, Gómez B, Gangoiti I, Hernández-Bou S, de la Torre Espí M; Bacteremia Study Working Group from the Infectious Diseases Working Group, Spanish Society of Pediatric Emergencies. Late-onset Group B Streptococcus Bacteremia Evaluated in the Pediatric Emergency Department and Risk Factors for Severe Infection. Pediatr Infect Dis J. 2022 Jun 1; 41 (6) 455-459* se estudiaron 134 pacientes diagnosticados de IBI por estreptococo grupo B. Sólo se encontró algún factor de riesgo en el 14,4% de los pacientes. En cuanto a la sensibilidad de los análisis de los diferentes marcadores sanguíneos para el diagnóstico de la infección grave, no se encontraron diferencias estadísticamente significativas, aunque se detectaron valores de procalcitonina superiores a 0,5 ng/ml en las infecciones más graves. De los 74 pacientes con infecciones graves (sepsis y/o meningitis) sólo 15 presentaron un TEP estable cuando fueron atendidos en el servicio de urgencias. El análisis multivariante identificó como único factor de riesgo independiente relacionado con la infección grave la situación de inestabilidad a la llegada a urgencias identificada mediante el TEP. En seis pacientes (5,1%) la evolución no fue buena, todos tuvieron complicaciones agudas graves

(5,1%), dos sufrieron secuelas persistentes y otros dos fallecieron. Los seis pacientes eran menores de 26 días, no estaban estables según el TEP y presentaron valores altos de procalcitonina y cuatro de ellos presentaron además leucopenia.

Los artículos que han analizado la recomendación de no utilizar de manera sistemática test sanguíneos a la hora de evaluar a los niños de 3 a 24 meses de edad, previamente sanos y con fiebre sin foco y buen estado general, son fruto de los resultados de dos trabajos que se desarrollaron con una metodología diferente.

El artículo de *Gangoiti I, Rodriguez E, Zubizarreta A, Benito J, Mintegi S. Prevalence of Occult Bacteremia in Infants With Very High Fever Without a Source. Pediatr Infect Dis J. 2018 Nov; 37 (11): e271-e273* es el resultado de un estudio retrospectivo, descriptivo y analítico realizado en un servicio de urgencias de Pediatría (SUP) de un hospital terciario que forma parte del Sistema Público de Salud. La población investigada fueron los lactantes previamente sanos de 3 a 24 meses de edad, estables y con una temperatura igual o superior a 40,5 ºC en su domicilio o en el hospital, atendidos en el servicio pediátrico de urgencias entre enero de 2013 y diciembre de 2016. La variable resultado fue la identificación de una bacteria patógena real. En total se recogieron 543 cultivos y posteriormente se realizó un análisis según el origen conocido o desconocido de la fiebre. La prevalencia de bacteriemia oculta entre 363 niños con fiebre sin focalidad se estimó en un 1,1% (IC 95%: 0-2,2). La evolución de todos ellos fue buena.

El artículo de *Gangoiti I, Zubizarreta A, Elgoibar B, Mintegi S; Infectious Diseases Working Group, Spanish Society of Pediatric Emergencies (SEUP). Occult bacteremia in young children with very high fever without a source: a multicenter study. Pediatr Infect Dis J. 2020 Dec; 39 (12):e462-e464* trata de una investigación prospectiva y multicéntrica (niños atendidos en 6 servicios de urgencias de pediatría españoles) y se basó en una

cohorte de pacientes previamente sanos y con temperatura igual o superior a 40,5 ºC, sin foco aparente. Los pacientes fueron reclutados prospectivamente desde el 1 de enero de 2018 hasta el 31 de diciembre de 2019. Los criterios de inclusión, el manejo terapéutico, las definiciones y la variable resultado que se plantearon en este estudio son los mismos empleados en la investigación unicéntrica comentada previamente.

En total se reclutaron 203 pacientes y en 31 pacientes se diagnosticó una infección bacteriana potencialmente grave: infección urinaria 14 (6,9%), neumonía 11 (5,4%) y bacteriemia 6 (3%). En 3 de los 6 niños diagnosticados de bacteriemia oculta se aisló un neumococo bien por cultivo o por técnicas de PCR; la prevalencia de bacteriemia oculta neumocócica se estimó en un 1,48% (IC 95%: 0,5-4,3). La evolución de todos los pacientes fue buena.

Todos los artículos recogidos en esta tesis inciden en que la investigación y vigilancia continuada de las IBI debería ser una actividad imprescindible para ofrecer la atención de mayor calidad al niño, niña y adolescente que pueda sufrir una enfermedad de este tipo. Aunque no fuera motivo esencial de esta tesis, el impacto de la pandemia COVID sobre la epidemiología de las IBI diagnosticadas en nuestro entorno confirma lo anterior.

INTRODUCCIÓN

La fiebre es un motivo habitual de consulta en pacientes atendidos en un SUP[1].

Aunque es cierto que lo más frecuente es que el origen de la fiebre sea una infección viral autolimitada, en ocasiones puede ser un síntoma inicial de una infección bacteriana invasiva (IBI). Para diagnosticar una IBI, una bacteria patógena debe ser identificada en sangre, líquido cefalorraquídeo, pleural o articular. La IBI que más preocupa es aquélla en la que se aísla el germen en sangre o líquido cefalorraquídeo, ya que la sepsis y la meningitis continúan siendo una causa de muerte no despreciable en los países desarrollados[2], a pesar de que las condiciones de vida y los estudios realizados en el campo de las vacunas y antibióticos en las últimas décadas, hayan supuesto importantes avances. Esto último ha provocado un notable descenso del aislamiento de las bacterias más comunes responsables de infecciones graves en los últimos años. Por otro lado, en los países desarrollados, es evidente el aumento de la accesibilidad de los servicios sanitarios de atención a pacientes y que los niños y niñas consultan con procesos infecciosos muy precoces, tanto en los servicios de urgencias hospitalarios como en atención primaria[3], siendo también muy frecuente que la edad de estos pacientes sea inferior a 2-3 años. Todo ello puede provocar cambios en la expresividad del cuadro clínico y favorecer que las características, signos y síntomas clásicos de presentación de las IBI décadas atrás, sean ahora menos visibles[4]. Además, el perfil del profesional médico que atiende al paciente pediátrico presenta una variabilidad muy elevada; desde un médico residente de primer año a un médico de familia de atención primaria que suele atender a pacientes adultos. Todas las variables de esta ecuación han influido en la identificación precoz de la IBI.

El impacto de las campañas de vacunación es incuestionable. Así, se ha visto claramente que la vacunación universal contra la *Haemophilus influenzae b*, que vino con el cambio de siglo, tuvo una consecuencia directa en una de las infecciones invasivas más graves que se identificaban en los niños del primer mundo[5], suponiendo su erradicación casi total en la población vacunada. Junto a esto, la comercialización de vacunas conjugadas frente a *Streptococcus pneumoniae* ha supuesto un descenso significativo de infecciones invasivas neumocócicas[3,6,7,8,9].

Era frecuente que, antes de la llegada de estas vacunas, en una pequeña proporción de lactantes previamente sanos con fiebre y buen estado general se aislara una bacteria en sangre (bacteriemia oculta), tanto *H. influenzae* como *S. pneumoniae*[10]. Según artículos clásicos, cuando la prevalencia de la bacteriemia oculta de una población era superior a la actual, se recomendaba la realización de hemocultivo a los niños de 3 a 24 meses con fiebre sin foco y temperatura superior a 39ºC[11]. Tras la implantación de las vacunas frente al *H. influenzae B* y *S. pneumoniae*, esta prevalencia ha disminuido drásticamente y la búsqueda sistemática de bacteriemia oculta no está recomendada en los niños que hubieran recibido al menos dos dosis de vacuna frente al neumococo[4,13,14,15,16,17,18]. De hecho, cuando la prevalencia de bacteriemia oculta baja del 0,5%, el rendimiento de las pruebas que se testan en sangre, como el recuento leucocitario y el número absoluto de neutrófilos, disminuye notablemente[11,19]. Y es que, según los datos que publicó Lee, el mayor rendimiento de estas pruebas de sangre se produce cuando la prevalencia de bacteriemia oculta supera el 1,5%.

También se sabe que la prevalencia de bacteriemia oculta aumenta cuando aumenta el valor de la temperatura objetivada[5] y se ha relacionado frecuentemente la gradación de la temperatura con la prevalencia de bacteriemia oculta. Las peculiaridades que ofrece el

grupo de niños con una temperatura muy elevada, generan dudas en cualquier profesional que esté a la cabecera del paciente.

Por otro lado, en las dos últimas décadas el número de infecciones invasivas causadas por *N. meningitidis* ha disminuido considerablemente[20,21], debido en parte al efecto que ha tenido la universalización de la vacuna frente a *N. meningitidis* del serogrupo C. La *N. meningitidis* del serogrupo B ha sido el principal causante de IBI en los países desarrollados en los últimos años. Sin embargo, recientemente otras variantes, especialmente W e Y, han ido ganando terreno, manteniéndose en general relativamente estable la tendencia del serogrupo B. En los últimos años, además, han aparecido en el mercado vacunas contra los diferentes serogrupos de *N. meningitidis*. El Consejo Asesor de Vacunas de la Asociación Española de Pediatría las ha recomendado[22] y algunas Comunidades Autónomas ya las han incluido en su estrategia postnatal financiada (en en el País Vasco se han beneficiado de esta medida niños nacidos en 2023), y su impacto está por ver.

Estos cambios no sólo han supuesto una importante reducción de las IBI, sino que indirectamente han provocado una mayor dispersión de los principales microorganismos causantes. Hoy en día, uno de los más importantes es la *E. coli*. Es el responsable de la mayor parte de las bacteriemias en niños menores de un año, especialmente en pacientes menores de tres meses y generalmente relacionadas con las infecciones de las vías urinarias[23]. Sin embargo, en nuestro entorno, no se ha llevado a cabo ningún estudio con una muestra amplia que analizara las características clínicas y las consecuencias de esta bacteriemia. Por lo tanto, está por dilucidar si existen diferentes perfiles de pacientes que sufren bacteriemia por *E. coli* y si estos diferentes perfiles están relacionados con un nivel de gravedad diferente.

Por todo lo expresado anteriormente, no es de extrañar que en ocasiones sea difícil la identificación precoz del niño que puede tener una IBI. El declive de las IBI en los últimos años, los cambios en las características de los pacientes atendidos (el paciente suele ser atendido en un servicio de urgencias antes de la aparición de los signos y síntomas más clásicos de los cuadros clínicos), y la gran variabilidad de los profesionales que atienden al niño en un servicio de urgencias, inciden en una mayor dificultad para identificar estas enfermedades. Un estudio afirmó que el 22% de los pacientes pediátricos que han sufrido meningitis bacteriana o sepsis consultaron en varias ocasiones un servicio de urgencias[24], aunque destacaron que los resultados y evolución finales fueron similares a los de los niños identificados en la primera consulta[25].

Sin embargo, las guías de manejo de la sepsis pediátrica han insistido en que el tratamiento antibiótico intravenoso rápido, cuando se ha visualizado el estado de shock y se ha implantado dentro de la primera hora, es clave[26]. Por ello, la respuesta a los análisis y biomarcadores de sangre de un determinado grupo de pacientes se convierte en una importante herramienta que forma parte del proceso de decisión para identificar la IBI. Si se tiene en cuenta que el cambio de microorganismos que habitualmente eran responsables de las IBI y que el proceso de atención al paciente es cada vez más precoz, el rendimiento y la respuesta de estos test será probablemente diferente a lo publicado clásicamente. En general, la leucocitosis y la neutrofilia han sido los parámetros analíticos más utilizados en la toma de decisiones en un servicio pediátrico de urgencias y más recientemente, la proteína C reactiva. En los últimos años, además, la procalcitonina ha actuado como un marcador bioquímico útil, ya que ofrece ventajas frente a los marcadores clásicos[16,17,27,28]. Sin embargo, la aparición y adición de nuevos biomarcadores puede dificultar en ocasiones la identificación de los pacientes con mayor riesgo de IBI[19], ya que no todas las infecciones influyen de la misma manera en los biomarcadores en sangre.

CLASIFICACIÓN DE LAS IBI

Como se ha mencionado en la introducción, el diagnóstico de IBI se basa en el aislamiento de una bacteria patógena en sangre, líquido cefalorraquídeo, líquido pleural o líquido articular. Sin embargo, dependiendo del líquido en el que se desarrolle el aislamiento, de su influencia en el huésped y de la respuesta que éste proporcione, pueden surgir situaciones clínicas muy diferentes.

La definición de bacteriemia consiste en el aislamiento de una bacteria patógena que se realiza en una muestra de sangre en pacientes previamente sanos. Se excluyen de esta manera los microorganismos que se definen clásicamente como contaminantes, como *Staphylococcus epidermidis, Propionibacterium acnes, Streptococcus viridans, Corynebacterium* spp., y otros difteroides. Los microorganismos denominados clásicamente contaminantes también pueden provocar bacteriemias en pacientes no previamente sanos: niños que sufren una enfermedad oncológica u otra inmunodeficiencia, pacientes portadores de catéter central o válvula de derivación, pacientes con técnicas diagnósticas o terapéuticas invasivas en los días posteriores a la realización de la extracción, ...

Dentro de la bacteriemia podemos distinguir dos grandes grupos: los producidos por una infección focal (infecciones focales invasivas) y los que carecen de infección focal (bacteriemia oculta).

Dada su importancia y gravedad, así como las tasas de mortalidad y morbilidad inexorablemente asociadas a las mismas, la meningitis (infección focal invasora) y la sepsis (infección diseminada que puede tener un origen focal conocido o desconocido) se exponen de forma específica.

Meningitis bacteriana

Se denomina meningitis a la inflamación de las meninges, que afecta a la piamadre, aracnoide y zona subaracnoidea. Respecto a su etiología, lo más frecuente en la edad pediátrica es el origen viral, sobre todo el enterovirus, cuyo pronóstico es muy bueno de forma general. La denominación bacteriana estará limitado al aislamiento de una bacteria que crece en el líquido cefalorraquídeo. Esta situación se produce, generalmente, después de que los organismos que han colonizado las capas mucosas, hayan invadido la circulación sanguínea.

Las campañas de vacunación de los últimos años y la profilaxis antibiótica que se realiza en torno al estreptococo del grupo B han cambiado radicalmente la epidemiología de la meningitis bacteriana. El estreptococo del grupo B o los Gram negativos serán causantes de la meningitis bacteriana en niños menores de tres meses y el *Streptococcus pneumoniae* y *Neisseria meningitidis* en niños sanos mayores de esta edad[29,30,31,32,33].

En la mayoría de los casos, las bacterias se extienden por los vasos sanguíneos y tras atravesar la barrera hematoencefálica pasan a la zona interior de la aracnoides. Una vez alcanzado el sistema nervioso, tras una replicación exponencial y la creación de numerosos intermediarios generadores de inflamación, se iniciará el proceso que dará lugar a la lesión definitiva del tejido. Aunque en la patogenia de la meningitis este mecanismo sea el más importante, también podrían provocar este cuadro clínico la trasmisión a partir de un seno nasal, del ojo o a través del hueso mastoides. Otras situaciones, como la fractura de cráneo con presencia de licuorrea o los procedimientos de neurocirugía o los causados por herida penetrante, también pueden facilitar el desarrollo de una meningitis.

Determinarán la clínica de meningitis, la edad del niño, los microorganismos causantes, los tiempos de evolución y la respuesta inmunológica del paciente. En los recién nacidos y lactantes más pequeños, la clínica suele ser poco específica: irritabilidad, rechazo a la ingesta, menor actividad, fiebre o hipotermia, cianosis e incluso apnea. Los síntomas de los lactantes mayores también son muy inespecíficos, con fiebre en la mayoría de los casos, irritabilidad, letargo, vómitos, rechazo a comer además de otros signos y síntomas. En los niños mayores y adolescentes son más habituales los síntomas más clásicos: fiebre, vómitos, fotofobia, dolor de cabeza...

Los signos clínicos que puedan destacarse en la exploración física del paciente con una meningitis también serán mucho más inespecíficos en los recién nacidos y lactantes pequeños. El hecho de que la fontanela esté abombada es un signo de hipertensión intracraneal, signo tardío de forma clásica, pero poco frecuente hoy en día. Así, según un estudio de Martínez et al[32], entre los 11 niños con meningitis menores de tres meses la fontanela era normal en diez y en uno no se indicó el estado de la fontanela. En los niños mayores pueden apreciarse los signos más clásicos de la meningitis: Kernig (respuesta rígida de la nuca provocada por la flexión de la cadera) y Brudzinski (respuesta rígida que ofrece la propia nuca al intentar su flexión). La rigidez de nuca tampoco es un signo patognomónico de la meningitis, ya que también se han descrito en otros procesos como neumonía, faringoamigdalitis o gastroenteritis[34,35]. Sin embargo, la mera aparición de estos signos aumenta la posibilidad de presencia de meningitis, siendo casi imprescindible la realización de pruebas para descartarla[30,34,36].

Las clásicas descripciones de las formas de presentación atribuibles a la meningitis también pueden ayudar a la identificación de su origen. Dentro de las meningitis bacterianas se han destacado dos variantes. Una, con un inicio abrupto y una evolución

continua y rápida, con shock, púrpura, coagulación intravascular diseminada, disminución de la consciencia, ... pudiendo llegar la muerte a las 24 horas del inicio de los síntomas; la segunda, algo más insidiosa, que viene tras unos días de fiebre, acompañada de síntomas del sistema respiratorio o del aparato digestivo y que revelará progresivamente signos más específicos de afectación del sistema nervioso central como irritabilidad o letargo.

Sepsis

Actualmente en pediatría no se ha establecido una definición concreta que sea aceptada por toda la comunidad científica; en general, llamamos sepsis a la disfunción orgánica que amenaza la vida causada por una respuesta desregulada del huésped a la infección[37].

De hecho, la última definición regulada que se utilizó en pediatría, es la adoptada en la Conferencia Internacional para el Consenso de la Sepsis Pediátrica celebrada en 2005[38]. Según esto, la sepsis es un síndrome sistémico de respuesta inflamatoria del organismo ante una posible infección y/o infección confirmada. Para su definición se utiliza la escala de puntuación SIRS (Systemic Inflammatory Response Syndrome/—Síndrome de Respuesta Inflamatoria Sistémica), con los siguientes parámetros: taquicardia no deducible por otro motivo y con relación a la edad (bradicardia en niños menores de un año), taquipnea según la edad, o proceso respiratorio agudo con necesidad de ventilación mecánica; temperatura superior a 38,5ºC o inferior a 36ºC y recuento anormal de leucocitos (leucocitosis o leucopenia) o recuento de neutrófilos inmaduros superior al 10%; siendo criterios obligatorios los criterios derivados del análisis sanguíneo o la temperatura[26,38].

Los criterios SIRS han sido muy criticados desde su creación. De hecho, no tienen la suficiente validez para realizar el diagnóstico de un cuadro de gravedad como la sepsis y

tienen baja sensibilidad y especificidad para predecir mortalidad. Por eso se ha utilizado con frecuencia el concepto de "sepsis grave" que se aprobó en este documento de consenso[38]. En ella, a la definición de sepsis se añadieron los siguientes criterios: disfunción cardiovascular, síndrome respiratorio agudo y/o disfunción de otros dos sistemas. El shock séptico fue definido como sepsis y disfunción orgánica no estabilizada con la administración de 40 ml/kg de líquidos isotónicos.

Todo ello llevó a Surviving Sepsis Campaign, a publicar en 2016 el "Sepsis-3, el tercer documento de consenso internacional"[39], dirigido al paciente adulto. Obviaron los criterios SIRS y simplificaron las definiciones a sepsis y shock séptico, eliminando el concepto sepsis grave. Definen la sepsis como una disfunción orgánica que provoca respuestas inmunes inadecuadas y pone en peligro la vida frente a una infección. En la valoración de esta disfunción orgánica se utiliza la escala SOFA (Sequential Organ Failure Assessment) y el diagnóstico de sepsis se establecerá en el caso de puntuaciones de 2 o superiores a 2.

Escala SOFA (Sequential Organ Failure Assessment)

	0	1	2	3	4
Respiración PaO_2/FiO_2 (mmhg) o SaO_2/FiO_2	>400	<400 221-301	<300 142-220	<200 67-141	<100 <67
Coagulación Plaquetas ($10^3/mm^3$)	>150	<150	<100	<50	<20
Hígado Bilirrubina (mg/dl)	<1,2	1,2-1,9	2,0-5,9	6,0-11,9	>12,0
Cardiovascular[b] Presión arterial (PA)	PA media ≥70mmHg	PA media TA<70mmHg	Dopamina <5 o dobutamina a cualquier dosis	Dopamina 5-15; adrenalina <0,1 o noradrenalina ≤0,1	Dopamina>15; adrenalina >0,1 o noradrenalina >0,1
Sistema nervioso central Escala de Glasgow	15	13-14	10-12	6-9	<6
Renal Creatinina mg/dl Flujo urinario (ml/día)	<1,2	1,2-1,9	2,0-3,4	3,5-4,9 <500	>5 <200

PaO_2, *presión arterial de oxígeno;* ***FiO_2****, fracción de oxígeno inspirado;* ***SaO_2****, saturación arterial de oxígeno periférico.* ***b****, Medicamentos vasoactivos administrados al menos durante una hora para mantener la presión arterial media >65mmhg (unidades: microgramo/kg/min)*

El shock séptico, en cambio, se definirá cuando confluyan un lactato > más de 2mmol/l y una disfunción cardiovascular que genere hipotensión persistente con necesidad de drogas vasoactivas.

En los últimos años se han realizado numerosos intentos de adaptar estas definiciones al ámbito pediátrico, planteándose también la escala denominada p-SOFA[40].

Tabla P-SOFA

	0	1	2	3	4
Respiración PaO_2/FiO_2 (mmhg) SaO_2/FiO_2	 >400 ≥ 292	 300-399 264-291	 200-299 14	100-199 con soporte respiratorio. 148-220 con soporte respiratorio	 <100 con soporte respiratorio <148 con soporte respiratorio
Coagulación Plaquetas ($10^3/mm^3$)	>150	100-149	50-99	20-49	<20
Hígado Bilirrubina (mg/dl)	<1,2	1,2-1,9	2,0-5,9	6,0-11,9	>12,0
Cardiovascular PAM (mmHg) o necesidad de drogas vasoactivas (mcg/Kg/min)	PAM <1 mes: ≥46 1-11 m: ≥55 12-23 m: ≥60 24-59 m: ≥62 60-143 m: ≥65 144-216 m: ≥67 >216 m: ≥70	PAM <1 mes: <46 1-11 m:<55 12-23 m: <60 24-59 m: <62 60-143 m: <65 144-216 m: <67 >216 m: <70	Necesidad de drogas vasoactivas: Dopamina ≤5 o dobutamina (cualquier dosis)	Necesidad de drogas vasoactivas: Dopamina 5-15 o adrenalina ≤0,1 o noradrenalina ≤0,1	Necesidad de drogas vasoactivas: Dopamina 5-15 o adrenalina ≤0,1 o noradrenalina ≤0,1
Sistema nervioso central Escala de Glasgow	15	13-14	10-12	6-9	<6
Renal Creatinina mg/dl					
<1 mes	<0,8	0,8-0,9	1,0-1,1	1,2-1,5	≥1,6
1-11 m	<0,3	0,3-0,4	0,5-0,7	0,8-1,1	≥1,2
12-23 m	<0,4	0,4-0,5	1,6-1,0	1,1-1,4	≥1,5
24-59 m	<0,6	0,6-0,8	0,9-1,5	1,6-2,2	≥2,3
60-143 m	<0,7	0,7-1,0	1,1-1,7	1,8-2,5	≥2,6
144-216 m	<1,0	1,0-1,6	1,7-2,8	2,9-4,1	≥4,2
>216 m	<1,2	1,2-1,9	2,0-3,4	3,5-4,9	≥5

Sin embargo, el último documento de actualización de la sepsis pediátrica publicado en 2020 no ha experimentado ninguna transformación significativa desde la definición de 2005[41]. Según los estudios llevados a cabo en las Unidades de Cuidados Intensivos, muestran que la escala pSOFA indica que, tanto a la hora de definir la disfunción orgánica como a la hora de realizar la previsión de las tasas de mortalidad, es más útil que los criterios SIRS[42].

NO obstante, el uso de esta escala en un SUP está fuertemente condicionado por los criterios de laboratorio, por lo que su aplicación no está extendida en este entorno. Las sociedades científicas pediátricas siguen trabajando para consensuar una definición que sea útil y práctica en todos los entornos sanitarios.

En cuanto a la epidemiología, las bacterias mencionadas anteriormente serán las principales responsables en pacientes sanos. El estreptococo del grupo B será el responsable más destacado de los shocks sépticos en niños más pequeños *y N. meningitidis* en pacientes mayores de 3 meses[43,44,45,46].

Infecciones focales invasivas

Infección de las vías urinarias

Cuando a determinados signos y síntomas se añade el aislamiento de un número significativo de bacterias en las vías urinarias diremos que estamos ante una infección urinaria. El diagnóstico definitivo vendrá determinado por la aparición de la leucocituria y el cultivo positivo en el análisis de orina.

Cuando hablamos de infecciones urinarias distinguiremos dos cuadros clínicos. Por un lado, pielonefritis aguda es la infección que afecta a las vías urinarias superiores. Suele presentar fiebre superior a 38,5ºC, elevación de los valores de los marcadores biológicos sanguíneos (como leucocitosis, neutrofilia, o velocidad de sedimentación globular, proteína C reactiva y procalcitonina) y puede derivar en una posible lesión renal irreversible como cicatrices en la corteza. La cistitis, por otra parte, es una infección que afecta a las vías urinarias inferiores, generalmente sin fiebre y asociada a los síntomas relacionados con la micción (dolor, polaquiuria, hematuria, ...). No provocará cicatrices en el riñón.

El principal signo de infección urinaria en los lactantes es la fiebre, que a menudo puede ser el único (algunos estudios indican que la fiebre fue el único signo en el 78% de los lactantes con crecimiento urinario positivo)[47]. Así, se puede entender fácilmente la dificultad de realizar un diagnóstico correcto si no se realizan pruebas.

El resto de síntomas pueden ser variados, irritabilidad, vómitos, estancamiento de la ganancia de peso, rechazo a la comida, ... Entre los recién nacidos, la infección urinaria también puede ser la causa de la ictericia que dura más de una semana[48].

Entre los pacientes de mayor edad, el cuadro clínico puede ser más preciso. Son frecuentes la disuria, la polaquiuria y en ocasiones puede aparecer hematuria. De hecho, la infección urinaria es la principal causa de hematuria en la infancia.

Cuando la infección afecta al riñón, además de la fiebre alta, puede aparecer dolor abdominal o lumbar y escalofríos. Durante el examen físico, la puño percusión renal suele ser dolorosa, indicativa de la inflamación de la capsula renal.

Escherichia coli es la bacteria que más se aísla en las infecciones de las vías urinarias; otras enterobacterias, especialmente las Gram negativas (*Klebsiella* y otras), suelen ser frecuentes en los aislamientos del cultivo urinario. En los lactantes pequeños la presencia de cocos gram positivos como *Enterococcus spp* puede ser habitual. En pacientes no previamente sanos, también podemos encontrar otras bacterias causantes, clásicamente relacionados con enfermedad más grave, aunque esto se haya puesto en duda en estos últimos años[49].

Cuando la bacteria responsable de la infección en las vías urinarias pasa a la corriente sanguínea, estaremos ante una bacteriemia. *E. coli* es la bacteria que más se aísla en la sangre en niños menores del año con fiebre, y más aún por debajo de los tres meses, en los que el origen de la bacteriemia es, en muchas ocasiones, la infección de las vías urinarias[50].

Sin embargo, y en general, la tasa de bacteriemia objetivada en lactantes con infección urinaria febril es baja. La excepción en nuestro entorno son los lactantes más pequeños,

observándose una tasa de bacteriemia del 11,3% en los niños menores de un mes, del 5,9% entre uno y dos meses y del 2,3% entre los que han cumplido dos meses[51].

Neumonía

Según la organización sanitaria mundial, la neumonía es la principal responsable de las muertes de niños menores de 5 años; la quinta parte de las muertes de niños de esta edad en países en desarrollo se deben a esta enfermedad. En los países desarrollados la situación es totalmente diferente; se trata de un diagnóstico relativamente frecuente pero que rara vez produce efectos graves y las tasas de hospitalización no son excesivamente altas, debido al éxito general del tratamiento antibiótico ambulatorio[52,53,54].

El diagnóstico debe estar basado en un proceso infeccioso que incluya síntomas respiratorios. El examen físico puede poner de manifiesto signos como áreas pulmonares de hipoventilación, estertores, crepitantes o soplo tubárico. No es obligatorio para el diagnóstico la imagen radiológica, pero en los países desarrollados es casi universal que la imagen radiológica confirme la sospecha diagnóstica. Lo más habitual es que el paciente pueda presentar una dificultad respiratoria leve.

Sin embargo, en determinados casos, ciertos aspectos fisiológicos básicos (el equilibrio hemodinámico, el nivel de consciencia, ...) estarán comprometidos. En estos casos, la gravedad será significativamente mayor, pudiendo llegar a cumplir los criterios de sepsis siendo imprescindibles las medidas de estabilización. Si el hemocultivo o la identificación del patógeno por técnicas de biología molecular es positivo, estaríamos ante una bacteriemia con una infección respiratoria en origen.

Aun así, la mayoría de las neumonías son causadas por virus, especialmente en niños menores de 5 años. Entre las bacterias, la principal responsable es *S. pneumoniae* a cualquier edad. Entre los niños mayores, la identificación de *Mycoplasma pneumoniae*

también es común. Otras bacterias que pueden ser responsables en niños previamente sanos son *S. aureus, S. pyogenes, C. pneumoniae* y *H. influenzae* no tipo b.

Entre los niños no previamente sanos, pueden ser responsables la *Legionella*, hongos oportunistas (Candida, Aspergillus…), *P. jiroveci,* otras bacterias anaerobias, … en pacientes con VIH, fibrosis quística u otro tipo de inmunosupresión[54,55].

Infección osteoarticular

Nos centraremos en la artritis séptica y la osteomielitis.

La artritis séptica es una emergencia ortopédica que requiere de una acción inmediata para evitar posibles complicaciones o secuelas persistentes. Se denomina artritis a la infección bacteriana de una o varias articulaciones, que puede aparecer a cualquier edad, con una mayor incidencia alrededor de los dos años. Normalmente se produce en una sola articulación, pero en los casos producidos por *N. meningitidi*s o *N. gonorrhoeae* son más frecuentes las poliartritis. Fiebre, irritabilidad, limitación para la movilización de la articulación, … son síntomas y signos habituales. *Staphylococcus aureus* suele ser el principal responsable cuando el cuadro sistémico es llamativo. *Salmonella* (en pacientes con anemia drepanocítica), *S. pneumoniae, Streptococcus pyogenes* (en personas que han pasado la varicela recientemente), o los mencionados previamente también son agentes que pueden producir artritis. Entre los niños recién nacidos y más pequeños la infección puede ser causada por estreptococo del grupo B y enterobacterias[56].

Kingella Kingae aparece en primer plano en el origen de las infecciones osteoarticulares en los últimos años. El cuadro clínico suele ser menos florido, la fiebre es menos frecuente, el estado general de los pacientes no es malo y la limitación para el movimiento es más sutil. Las nuevas técnicas de laboratorio han permitido detectar la presencia de

esta bacteria[57]. Hoy en día, es la principal causa de artritis séptica entre los 4 meses y los 4 años de edad.

La osteomielitis, por su parte, suele ser una infección que se localiza en el lado metafisario del hueso y que puede pasar a la médula ósea, invadiéndola. La lista de agentes causantes es muy similar[56,57].

La propagación de estas infecciones al torrente sanguíneo puede producirse tanto por efecto de pared a pared como por paso directo. Cuando el aislamiento de esta bacteria causante de la infección osteoarticular se realiza también en sangre, nos referiremos a la bacteriemia que tiene origen en una infección osteoarticular.

Infección de piel y tejidos blandos

Como su nombre indica, en este grupo recogeremos las infecciones bacterianas de las diferentes capas que componen la piel y también de otros tejidos como tendones, músculos, etc. Entre ellas, podemos encontrar al impétigo, la celulitis, la foliculitis, la linfangitis, … que son muy comunes y habitualmente de poca gravedad. Por otro lado, podemos tener erisipela, forunculosis o abscesos que pueden conllevar mayor gravedad. Por último, la piomiositis y la fascitis necrosante van a requerir un tratamiento más agresivo y en los casos más graves será imprescindible el tratamiento quirúrgico. En general, el origen de la infección se debe a una herida o lesión que se ha originado en la piel; pocas veces se deberá a una infección que se ha extendido desde otro sistema del organismo.

Los principales responsables serán las bacterias que conviven habitualmente en la piel, principalmente *S. aureus* y *S. pyogenes*. Se considerarán situaciones especiales los casos de heridas en agua (*P. aeruginosa, A. hydrophila y V. Vulnificus*), mordeduras (*P. multocida* y anaerobios), neonatales (estreptococo del grupo B y Gram negativos),

pacientes inmunosuprimidos (*P. aeruginosa*, enterobacterias y otros Gram negativos) y casos como la fascitis necrosante (*Clostridium* y otros anaerobios)[58,59].

Mención aparte merecen síndromes producidos por las toxinas de *S. aureus* y *S. pyogenes*: síndrome de piel escaldada y shock estafilocócico en el caso de *S. aureus* y shock estreptocócico en el caso de *S. pyogenes.*

El síndrome de la piel escaldada (síndrome de Ritter) ocurre a partir de una infección local que *S. aureus* ha originado en la piel. La fiebre brusca, la irritabilidad y un rash doloroso que puede ser inicialmente escarlatiniforme serán los síntomas más llamativos. Esta erupción cutánea asociará el desarrollo de bullas uno o dos días después para ser totalmente denudadas posteriormente. En el caso del shock las toxinas estafilocócicas actuarán como superantígenos. Fiebre brusca, vómitos, diarrea, mialgias, eritrodermia e hipotensión serán los signos y síntomas más destacados. El tratamiento de estabilización y sostén junto a la antibioterapia intravenosa serán claves[60].

El shock estreptocócico se produce en pacientes jóvenes y se han relacionado factores de riesgo significativos como varicela, diabetes mellitus, enfermedad respiratoria crónica, cardiopatía o VIH. Se trata de una enfermedad con una alta tasa de mortalidad, definida por signos y síntomas como la hipotensión, fiebre, eritrodermia y el compromiso multiorgánico. Para su diagnóstico son necesarios criterios clínicos, microbiológicos y analíticos[61].

Globalmente, en las infecciones de piel y tejidos blandos, el rendimiento de los cultivos sanguíneos en pacientes estables y previamente sanos suele ser muy bajo. En el caso de aislamiento positivo en sangre, hablamos de bacteriemia cuyo origen es una infección de piel y tejidos blandos.

Bacteriemia oculta

La bacteriemia oculta es el aislamiento de una bacteria real en la sangre del paciente que tiene buen estado general y no presenta ningún signo ni síntoma además de la fiebre.

El adjetivo “oculta” hace referencia al estado del paciente, es decir, el niño debe tener un buen estado general. Para definirlo se pueden utilizar varias herramientas, uno de ellos es el Triángulo de Evaluación Pediátrica, TEP, cuyo resultado cuando se interpreta como "estable" se entiende que el niño tiene un aspecto saludable[62].

El TEP es una herramienta rápida y muy útil para la evaluación inicial del paciente pediátrico. Su aplicación es sencilla, ya que no requiere estetoscopio, otoscopio u otros instrumentos más allá de la visión y audición del médico, enfermero o técnico formado. Esta herramienta trata de estructurar la valoración subjetiva que hace cada profesional sanitario cuando ve por primera vez a un paciente. En la mayoría de los centros hospitalarios donde se utiliza el triángulo de evaluación pediátrica, su evaluación se realiza en el triaje por el personal responsable de esta tarea en el centro (médicos y enfermeras). Como su nombre indica, se compone de tres lados: aspecto del paciente, trabajo respiratorio y circulación cutánea. El triángulo de evaluación pediátrica no nos da un diagnóstico del paciente, pero sí nos informa de las necesidades urgentes que tiene el paciente para mantener un estado fisiológico y homeostasis adecuados.

Por otro lado, el paciente no debe presentar signos o síntomas que puedan indicar el origen de la fiebre, tales como tos, diarrea, inflamación de amígdalas, auscultación patológica, polipnea, signos meníngeos, etc.

Según la bacteria sospechosa, la probabilidad de que una bacteriemia progrese a una meningitis es diferente (en el caso de *H. influenzae* y meningococo es mayor que con el neumococo). Una vez administrada una única dosis de antibiótico parenteral, la

probabilidad de que avance la bacteriemia producida por el neumococo es limitada[11]. Esta es la principal razón de los esfuerzos que se hacen para buscar la bacteriemia oculta. Como ya se ha mencionado, los cambios en el contexto epidemiológico, en los hábitos sociales, y sobre todo el hecho de que los pacientes con mayor riesgo de bacteriemia oculta sean en general los más pequeños, hace que su identificación sea dificultosa. En las últimas décadas se han realizado grandes intentos para identificar grupos de pacientes previamente sanos susceptibles de padecer una bacteriemia oculta.

BACTERIAS MÁS IMPLICADAS EN LAS IBI DE LA INFANCIA

Streptococcus pneumoniae

Streptococcus pneumoniae es un coco Gram positivo que forma cadenas cortas. Se conocen más de cien serotipos diferentes y cada uno de ellos está definido por la cápsula polisacárida. De esta última depende la inmunidad específica de cada serotipo. Esta bacteria inicia la colonización de la vía nasofaríngea en los primeros meses de vida, alcanzando su máximo nivel de colonización a los 3 años. Para entonces, entre el 25% y el 80% de la población infantil estará colonizada. *Streptococcus pneumoniae* puede producir dos tipos de infecciones: IBI (meningitis, bacteriemia, sepsis, neumonía bacteriémica y otras) y no invasivas (neumonía no bacteriémica, otitis o sinusitis por ejemplo).

La colonización de las vías nasofaríngeas constituye el único reservorio de *Streptococcus pneumoniae,* lo que facilita la dispersión tanto familiar como comunitaria[63].

A finales de los años 90, *Streptococcus pneumoniae* era el principal responsable de la meningitis bacteriana entre los niños. Sin embargo, en las últimas décadas, las vacunas conjugadas comercializadas han tenido un gran impacto epidemiológico; su prevalencia ha descendido drásticamente en los países que se consideran desarrollados. Todo ello ha supuesto un cambio en la aproximación diagnóstico-terapéutica ante los niños febriles en los servicios de urgencias pediátricos[64].

Neisseria meningitidis

Neisseria meningitidis es un microorganismo diplococo Gram negativo. El humano es el único reservorio de esta especie y suele aislarse en la vía buconasofaringea (los

porcentajes de portadores son muy variables). *N. meningitidis*, junto con *N. gonorrhoeae*, son las únicas especies patógenas del género Neisseria.

Antigénicamente se divide en al menos 13 serogrupos, caracterizados por el polisacárido de la cápsula de la *Neisseria meningitidis*. Históricamente han sido los grupos B y C los que han originado las enfermedades meningocócicas de los países occidentales, aunque los serogrupos Y o W135 han experimentado un aumento relativamente notable durante los últimos años. Por otro lado, el serogrupo causante de epidemias es el A, especialmente en los países en vías de desarrollo.

La epidemiología de la enfermedad meningocócica invasora es generalmente muy variable. A lo largo de la historia ha vivido diferentes olas y desde que los datos son accesibles y públicos, la incidencia más baja de la enfermedad se ha situado a mediados de la última década[65,66].

Sin embargo, en la última mitad de la década de 2010 comenzó a detectarse un cierto aumento generalizado, no sólo en nuestro entorno; además los responsables no eran especialmente los serogrupos B y C. Según algunos expertos, podríamos encontramos ante una onda epidémica, pero debido a las medidas que se impusieron ante la pandemia de Sars-Cov-2 de 2020 (sobre todo la mascarilla y las medidas de distanciamiento), la incidencia de ciertas enfermedades infecciosas transmisibles se redujo de manera sustancial, y entre ellas la de la enfermedad meningocócica invasiva[67,68].

Las formas más frecuentes de infección invasiva por *Neisseria meningitidis* son la meningitis, la sepsis o la combinación de ambas. El plazo de incubación suele ser de 3-4 días. Aunque no es fácil de calcular, las sepsis meningocócicas que no producen meningitis oscilan entre el 5 y el 20%. La sepsis tiene un comienzo brusco, además de la fiebre aparecen lesiones llamadas petequias, que aumentan en poco tiempo, asociadas a

menudo a hipotensión, shock o fracaso multiorgánico. La mortalidad de esta enfermedad sigue siendo alta (establecida en un 10% por las publicaciones clásicas) a pesar del gran avance de las técnicas diagnósticas y de tratamiento; la tasa de mortalidad es mayor en el caso de sepsis que en el de la meningitis[30,31,46,63].

Los picos de incidencia más significativos se dan en niños y niñas menores de 1 año, en edades de 1 a 4 años y en adolescentes de 15 a 19 años. Aunque pueden producirse a lo largo de todo el año, suelen acumularse en invierno y primavera tras la aparición del virus de la gripe. Ya lo hemos dicho anteriormente, pero los adultos portadores de *Neisseria meningitidis* en la vía buconasofaríngea pueden ser entre un 1% y un 15% y serlo además durante semanas o meses. Esta colonización puede conducir al paciente pediátrico no inmunizado a situaciones de alto riesgo.

Escherichia coli

Escherichia coli es una de las bacterias más investigadas históricamente. Es un bacilo Gram negativo de la familia de las enterobacterias, que forma parte de la flora bacteriana colorrectal y que en la mayoría de los casos no es patógena. Sin embargo, algunas cepas han adquirido factores de virulencia, por lo que pueden producir infecciones en humanos y animales. Pueden ocasionar diferentes signos y síntomas; los podemos agrupar en los siguientes cuadros clínicos: infección de vías urinarias, diarrea/gastroenteritis aguda, bacteriemia y sepsis/meningitis.

Tras la colonización de la mucosa de las vías urinarias por *Escherichia Coli*, prolifera en su interior, evitando las defensas del huésped. Se han designado varios factores de virulencia que favorecerán el síndrome clínico, especialmente la infección en las vías urinarias, las fimbrias P y S, la hemolisina, ...[69,70]

Pueden ser también causantes de diarrea/gastroenteritis aguda, que clasificarán en función del factor genético que marcará su virulencia y el cuadro resultante, los llamados patotipos. Entre ellos se encuentran los *E. coli* enteropatógenos, enteroinvasivos, enterotoxigénicos, ... [71]. Esta clasificación no es uno de los objetivos de este trabajo.

En general, *E. coli* es la bacteria más frecuente que se aísla en sangre junto con *S. pneumoniae* en niños menores de 12 meses[72], siendo la más habitual en el grupo de menores de 3 meses. Junto a las infecciones urinarias que causan bacteriemia, que es el diagnóstico más frecuente, *E. coli* también es causante de bacteriemias ocultas, pero también de sepsis y meningitis en los pacientes más jóvenes[50].

Los causantes de la meningitis serán los microorganismos que han colonizado capas mucosas. La patogenia de la meningitis bacteriana dependerá de la edad del huésped; en el caso de los recién nacidos, serán causantes en gran medida los patógenos que se hayan adquirido durante el parto como consecuencia de la absorción o contacto con las secreciones del canal del parto de la madre. Algún antígeno, como el antígeno de la cápsula K1 de *E. Coli,* es muy similar al polisacárido de la cápsula de *N. meningitidis* del serotipo B, que le permite llegar a traspasar la barrera hematoencefálica[73].

Staphylococcus aureus

Staphylococcus aureus es un coco Gram positivo, anaerobio facultativo, que forma parte de la microbiota humana habitual. Puede colonizar selectivamente orificios nasales, periné, axilas y pliegues cutáneos. En la actualidad, es la bacteria que más IBI produce en el grupo de pacientes previamente sanos pediátricos de más de 5 años de edad y es también la principal causante de las infecciones osteoarticulares y de piel y tejidos blandos[74,75]. Además, *S. aureus* es también responsable de las toxinas causantes del shock estafilocócico y del "síndrome de piel escaldada/síndrome de Ritter".

Las enfermedades causadas por *S. aureus* se dividen actualmente en dos grandes grupos. Por un lado, las enfermedades relacionadas con los hospitales y centros de salud y las que se producen fuera de estos ámbitos, es decir, en la sociedad comunitaria.

De hecho, se trata de una bacteria que preocupa mucho en el área hospitalaria y en los pacientes no previamente sanos, como los pacientes con dispositivos, catéteres o válvulas de derivación. Además, las bacteriemias en pacientes hospitalizados son mucho más frecuentes que las bacteriemias con foco[76], como las que se producen en pacientes previamente sanos y ajenos a los centros de salud cuyo origen son infecciones óseas y articulares, tejidos blandos y cutáneas y en menor proporción neumonía.

Otra característica que ha generado una gran preocupación es el *S. aureus* resistente a la meticilina (SAMR), inicialmente restringido al hospital y que ha demostrado capacidad de afectar fuera del mismo. Hay muchos estudios en marcha con el objetivo de conocer la incidencia del SAMR en la comunidad. Según un estudio retrospectivo que se llevó a cabo en nuestro entorno, la incidencia se sitúa en torno al 16%[77].

Estreptococo del grupo B

El estreptococo del grupo B es el segundo mayor responsable de las infecciones bacterianas invasivas que se diagnostican en niños menores de 3 meses tras el *E. coli*, pero es el principal causante de la sepsis y meningitis que se producen a esta edad[43,44,45].

Es un coco Gram positivo beta-hemolítico y hasta la fecha se han identificado 10 serotipos. Suele colonizar el tubo digestivo y el canal de parto, pudiendo ser provisional o permanente. El aparato digestivo como reservorio es una característica tanto para hombres como para mujeres[78].

Entre el 40 y el 60% de las mujeres colonizadas pueden transmitir esta bacteria a su recién nacido. Esta transmisión es directamente proporcional a la densidad de colonización de la mujer embarazada e inversa a la concentración de anticuerpos. El 1-2% de estos bebés recién nacidos desarrollará una infección que puede tener importantes tasas de mortalidad y morbilidad[79,80,81,82].

Las estrategias establecidas en los últimos años, como la prueba de screening que se realiza en el último trimestre del embarazo para la detección del estreptococo del grupo B y los protocolos de antibioterapia establecidos durante el parto, han influido directamente en la desaparición de las infecciones precoces que provoca esta bacteria. Sin embargo, no ha tenido el mismo efecto beneficioso en infecciones invasivas que se diagnostican más allá de los 7 días[83,84]. Esto puede deberse, por un lado, a que la colonización es transitoria y que en el cribado no se haya podido identificar la bacteria; y por otro, aunque no esté del todo claro, que el recién nacido haya permanecido en contacto y/o haya absorbido fluidos del aparato digestivo o reproductivo de la mujer que ha dado a luz[78].

Aunque no es la principal responsable de las bacteriemias que se identifican a esta edad, es la bacteria que produce los cuadros clínicos más graves. Su virulencia tiene origen en la capacidad de evitar la fagocitación que le proporciona el polisacárido de la cápsula[86,87].

Streptococcus pyogenes

El denominado *Streptococcus pyogenes* o beta hemolítico del grupo A es un coco Gram positivo que se une en cadenas (expresa antígenos A en la pared celular y contiene estreptolisinas S y O que dan lugar a hemólisis beta). Produce infecciones de piel y tejidos blandos, infecciones otorrinolaringológicas, neumonía, pero también infecciones de tejidos profundos, músculos, etc. que pueden ser graves (como la fascitis

necrotizante)[58,59]. Cuando se aísla en sangre, hablamos de bacteriemia. En pacientes pediátricos puede provocar bacteriemia oculta, aunque no es la presentación más frecuente; en pacientes adultos tiene una gran importancia[88]. Hay presentaciones más excepcionales, pero con una alta tasa de mortalidad, como es el shock tóxico estreptocócico provocado por toxinas que produce *S. pyogenes.*

Haemophilus influenzae

Este cocobacilo Gram negativo es un anaerobio facultativo. Históricamente esta bacteria se ha dividido en dos categorías, las capsuladas y las no capsuladas. La cápsula es la característica que le ha dado el principal factor de virulencia y ha sido históricamente la *H. influenzae* del tipo B, una de las principales responsables de las infecciones bacterianas más graves hasta que apareció la vacuna conjugada contra ella. En el caso de EE. UU. se pasó de 20.000 casos al año a menos de 40 para la primera década de 2000. Además del tipo B, existen otros 5 serotipos dentro de este germen encapsulado, que producen principalmente infecciones de vías respiratorias superiores e inferiores e infecciones otorrinolaringológicas. Estas cepas actúan generalmente como patógenos oportunistas. También es conocido que, del mismo modo que *S. pneumoniae*, el número de niños menores de 5 años portadores de *H. influenzae* es significativo.

Es cierto, sin embargo, que en la segunda década del siglo XXI las infecciones invasivas por *H. influenzae* han aumentado, tanto las serotipables como las que no lo son (sin cápsula)[89,90].

Otras bacterias

En el caso de *Salmonella*, el descenso de *S. pneumoniae* en las últimas décadas ha provocado un aumento del número relativo de aislamientos que han aparecido en las

muestras de sangre, especialmente en pacientes previamente sanos. Sin embargo, no se han destacado cambios significativos en los números absolutos[64,91].

El otro gran grupo que va cobrando cada vez más importancia es el que forman otros microorganismos (como *P. aeruginosa*) en el caso de las infecciones bacterianas en pacientes no previamente sanos; como son las bacterias que forman parte de nuestra microbiota o que en otras situaciones habituales se considerarían aislamientos contaminados (*Staphylococcus epidermidis* y otros *S. coagulasa negativo*, *S. viridans* y similares, *Propionibacterium acnes*, *Corynebacterium* spp., y otros *diphtheroide*s, ...). Aunque el objetivo de esta tesis no es investigar estas infecciones, sí habrá algunas explicaciones y comentarios a lo largo del texto.

RECURSOS DEL SERVICIO DE URGENCIAS PARA LA EVALUACIÓN DEL PACIENTE SOSPECHOSO DE IBI

Dependiendo del conjunto de signos y síntomas que presenta el paciente, en el servicio de urgencias tendremos a nuestra disposición una serie de herramientas y recursos para realizar el manejo más adecuado e individualizado del paciente sospechoso de IBI.

Test de sangre, en orina y en líquido cefalorraquídeo

Los análisis en sangre, orina y líquido cefalorraquídeo son los test complementarios habituales cuando emerge la sospecha de una infección bacteriana invasiva y constituyen el primer proceso de cribado en el manejo del paciente. Los analizaremos uno a uno.

Reactantes sanguíneos

Un biomarcador en sangre es una molécula que puede cuantificarse en una muestra sanguínea que puede ser indicativa del estado normal o patológico de un proceso biológico. La monitorización del proceso se definirá en función de la concentración que presente en sangre[92].

Por eso, los reactantes sanguíneos, tanto clásicos como los más modernos, tienen su espacio cuando estamos ante un paciente sospechoso de padecer una infección bacteriana ya que los resultados estarán disponibles en un breve espacio de tiempo. Los incrementos de sus concentraciones se han asociado a diferentes tipos de infección bacteriana, según el caso. Como todos los test que se realizan, tienen ciertas limitaciones, ya que las infecciones virales, que tendrán un manejo totalmente diferente, también pueden provocar cambios en estos test.

Los leucocitos y neutrófilos no cumplen con la definición exacta de biomarcador, pero en la práctica pueden asumir una función similar y por eso los incluiremos en este grupo de test y a partir de este momento hablaremos de biomarcadores.

Recuento leucocitario y número absoluto de neutrófilos

La infección bacteriana se ha asociado tradicionalmente con un aumento del recuento leucocitario y, específicamente, al número absoluto de neutrófilos. Se ha investigado mucho sobre estos reactantes; los puntos de corte más utilizados para la identificación del paciente con mayor riesgo de bacteriemia oculta, sobre todo neumocócica, han sido 15.000 leucocitos y 10.000 neutrófilos, respectivamente, por microlitro[11]. Sin embargo, debido a su bajo valor predictivo, basar la decisión de aplicar tratamiento antibiótico con estos resultados implicaría un sobretratamiento excesivo[18,93,94]. Mientras que algunos autores han llegado a la conclusión de que el número absoluto de neutrófilos es un test más exacto, en general se cree que tiene un perfil similar[95].

Proteína C reactiva

Es un biomarcador que sintetiza el hígado como respuesta al aumento de citoquinas por inflamación. El hígado comienza a sintetizarlo entre 4 y 6 horas después de la aparición de la inflamación y alcanzará su valor máximo en 36 horas.

Los puntos de corte asociados al diagnóstico de una infección bacteriana difieren según la edad. La literatura científica admite valores de 10 a 15 mg/l en niños recién nacidos y de 20 a 40 mg/l en niños más mayores. Sin embargo, también se ha demostrado que la inflamación por infecciones virales aumenta los valores de la Proteína C reactiva.

Varios estudios describían una sensibilidad similar a la procalcitonina a la hora de identificar la infección bacteriana. Sin embargo, su especificidad es mucho más baja[96]. Por otro lado, según diversos estudios, comparándolo con el recuento leucocitario y el

número absoluto de neutrófilos, se ha llegado a la conclusión de que tiene un valor predictivo más alto. Sin embargo, a la hora de decidir podría ser preferible combinarlo con otros biomarcadores, ya que este biomarcador por sí solo ha mostrado importantes limitaciones[94,95].

Procalcitonina

La procalcitonina es la precursora de la calcitonina, molécula sintetizada en pequeñas cantidades por las células C de la tiroides y las células neuroendoteliales pulmonares en situaciones normales. Ante una infección, su concentración sanguínea aumentará, ya que otros tejidos se encargarán de su síntesis, como el bazo, los testículos, el tejido graso y el cerebro. En comparación con la proteína C reactiva, el aumento de la concentración de procalcitonina en el torrente sanguíneo es mucho más rápido.

La procalcitonina es el biomarcador que mayor rendimiento ofrece para la identificación de infecciones bacterianas invasivas según diversos estudios realizados a lo largo de los años[27,98,99,100].

A pesar de la controversia persistente sobre los puntos de corte y de que la concentración de 2 ng/ml es la más descrita en pediatría, los últimos estudios abogan por concentraciones de 0,5 ng/ml[98].

Análisis de orina

La infección urinaria es una infección bacteriana con alta prevalencia, especialmente en niños menores de dos años[101]. La presencia de leucocituria o nitrituria o una tinción de Gram positiva sustentarán la sospecha diagnóstica. Una vez confirmada la sospecha, el cultivo de orina recogido de manera estéril deberá demostrar el aislamiento de una bacteria[102,103].

Tira reactiva de orina

Se trata de una prueba complementaria, sencilla y barata, que permite realizarla a la cabecera del paciente, dar un resultado inmediato y realizar una interpretación rápida, por lo que será un test que encontraremos a menudo en los algoritmos de diagnóstico y manejo. Existen numerosos estudios que comparan la tira reactiva (tanto leucocituria como nitrituria) con un urocultivo positivo[102].

Este test en sí mismo no indica explícitamente la presencia de leucocitos; es decir, es capaz de identificar la esterasa que desprenden los leucocitos en la orina debido a la inflamación[104]. La sensibilidad que ofrece este test para que el urocultivo sea positivo es del 83%, con una específicidad del 79% y un valor predictivo positivo del 89%. La nitrituria, en cambio, tiene un valor predictivo muy alto (95%), pero hay bacterias que no son capaces de producir nitritos y que pueden ser habituales en los análisis de orina (enterococos, *Staphylococcus* o *Pseudomona*). El sedimento y la tira reactiva han sido comparados por numerosos estudios. Esta última se considera un test adecuado para el screening en pacientes con riesgo de infección urinaria, ya que ofrece buen rendimiento, es rápido, muy barato y es un recurso disponible en la cabecera del paciente[105,106].

Además, se ha publicado que la presencia de nitrituria en los niños más pequeños es un factor de riesgo independiente de una infección invasiva[107].

Análisis citoquímico del líquido cefalorraquídeo

El análisis del líquido cefalorraquídeo (LCR) es un estudio imprescindible para el diagnóstico de la meningitis. Se trata de un análisis a realizar en todos los pacientes con sospecha de meningitis, siempre que el estado del paciente lo permita.

El LCR normal se caracteriza por ser incoloro, sin olor, con forma de agua destilada, pero con varios componentes que conforman la sangre. Si se presta atención a su análisis

bioquímico, se deduce que contiene proteínas; sí, pero, en una proporción 200 veces inferior al plasma; la glucosa, por su parte, oscilará entre el 50% y el 75% de la concentración presente en suero sanguíneo. El recuento de leucocitos de LCR también varía en función de la edad del paciente. Aunque es un tema controvertido, lo más aceptado es que en niños menores de un mes el punto de corte de la pleocitosis sea de 20 a 25 células/mm^3 y a partir de esta edad sea 10 o 5 células/mm^3. Además, la mayoría de los leucocitos serán linfocitos o monocitos[108]. Por tanto, será imprescindible analizar las características bioquímicas del LCR en el manejo terapéutico del paciente bajo sospecha de meningitis. Las variaciones en las características habituales serán indicativas de inflamación. En términos clásicos, la sospecha de meningitis viral o bacteriana solía establecerse conscientes de estas características. El LCR no claro, la pleocitosis con predominio de neutrófilos, la glucorraquia baja, así como la alta concentración de proteínas incrementa el riesgo de una meningitis bacteriana. Sin embargo, en la práctica cotidiana, no se ha observado que estas características muestren limitaciones[109,110]. Además, el LCR del paciente sospechoso de meningitis que haya recibido previamente antibiótico podría sufrir alteraciones como un cierto aumento de glucosa o una reducción de proteínas, aunque es frecuente que el número de leucocitos o neutrófilos no sufra variación[111].

Herramientas para la identificación de microorganismos

Clásicamente, el test más útil para evidenciar la presencia de infección bacteriana era el crecimiento de microorganismo en el cultivo de la muestra tomada en diferentes medios (sangre, líquido cefalorraquídeo, orina u otro). Pero el crecimiento de la bacteria necesita su tiempo. Existen otras técnicas más rápidas y con un rendimiento no inferior, disponibles en un servicio de urgencias que podrían influir en la capacidad de decisión

como son la tinción de Gram y los test que se basan en la técnica de reacción en cadena de la polimerasa.

Cultivos

El torrente sanguíneo, la orina (en general) y el LCR son, en sí mismos, estériles. En consecuencia, cuando se aísla una bacteria patógena en una muestra de sangre, se define que estaremos ante una bacteriemia. Además del diagnóstico etiológico, el cultivo permitirá realizar test de sensibilidad a los antimicrobianos y su tipificación. El cultivo necesitará entornos de cultivo adecuados, tanto para bacterias aerobias como anaerobias y será el "gold standard" para el diagnóstico microbiológico. Sin embargo, deberá pasar un tiempo mínimo de reproducción para que el aislamiento (mínimo 24 horas) logre un crecimiento significativo. Esto dificulta el manejo que se lleva a cabo en la cabecera del paciente pediátrico que es atendido en un servicio de urgencias.

En cuanto al cultivo del LCR, éste sigue siendo el patrón oro en el diagnóstico de la meningitis bacteriana y al igual que los casos de los hemocultivos, además del diagnóstico etiológico, permitirá la realización de test de sensibilidad de los antimicrobianos y la tipificación del germen. El procesamiento del LCR debe ser inmediato, inferior a una hora[112]. Posteriormente, el crecimiento tardará más de 24 horas en poder detectar la reproducción del germen. La rentabilidad del cultivo dependerá, además, de la bacteria responsable y de la no recepción de antibioterapia previa. En el 90% de las meningitis por neumococo se estima que el crecimiento será positivo al igual que en el 75% de las meningitis meningocócicas[113]. Algunos investigadores concluyeron que una sola dosis de ceftriaxona (dosis de 50 mg/kg) podría esterilizar el LCR de la meningitis meningocócica en una media de dos horas, la neumocócica en 4-10 horas y la del estreptococo del grupo B en 8 horas[30,114].

En cuanto a la infección urinaria, la prueba de oro que la confirmará será el urocultivo[115]. Para evitar falsos positivos (sobre todo por errores en el procedimiento de toma de muestra), la recogida de orina debe ser lo más adecuada posible: orina espontanea e instantánea (en pacientes con control vesical) una vez tomadas las medidas higiénicas adecuadas y sondaje vesical o punción suprapúbica en el resto. La concentración de bacterias que se aísla también debe ser significativa, si bien la Academia Pediátrica Americana o la Asociación Española de Pediatría difieren en pequeños detalles[116,117].

También podrán realizarse otros cultivos en los servicios de urgencias. En cada caso, y dependiendo del estado del paciente, el análisis de una u otra muestra puede ser importante. Por ejemplo, si se sospechara una infección de piel y tejidos blandos, podría ser interesante realizar un cultivo de una lesión susceptible de drenaje, ya que la rentabilidad de los hemocultivos en estos casos es muy baja, sobre todo en pacientes pediátricos previamente sanos y estables.

Además de estas lesiones susceptibles de drenaje, el cultivo de líquido sinovial, derrames pleurales u otros fluidos también puede tener su lugar en el manejo diagnóstico de un paciente (muchos de estos procedimientos no se realizarán estando el paciente en el servicio de urgencias).

Para el diagnóstico de una infección causada por el estreptococo del grupo A, el cultivo faringoamigdalar puede ser adecuado; y en las infecciones del aparato digestivo que pudieran provocar invasividad, el coprocultivo.

Tinción de Gram

La tinción de Gram en LCR se caracteriza por una gran especificidad, pero una sensibilidad media para el diagnóstico de meningitis bacteriana[118]. Sin embargo, la baja prevalencia de meningitis hace que el valor predictivo positivo sea muy escaso[119].

Además, la capacidad de visualizar bacterias por microscopio en el LCR dependerá de la propia bacteria y de la concentración de la misma. El 90% de los pacientes con meningitis neumocócica tendrá una tinción positiva, el 80% en meningitis meningocócica, el 50% en las causadas por bacilos Gram negativos y el 33% en las causadas por *Listeria monocitogenes*[30].

En el caso de la tinción de Gram en orina, la técnica se realizará inmediatamente después de recoger la muestra de orina recién realizada. Se trata de una prueba de alta especificidad (por encima del 99%), pero al ser una prueba que requiere mayores recursos no siempre está disponible[120]. Será, por tanto, un test que se utilizará en el manejo de pacientes individualizados.

Nuevas técnicas microbiológicas

En los últimos años se han comercializado nuevas técnicas microbiológicas que han ocupado un lugar destacado en los algoritmos de diagnosis y manejo de infecciones bacterianas y virales. Las técnicas diagnósticas basadas en la reacción en cadena de polimerasa son el ejemplo más conocido. Además, estas nuevas técnicas se han utilizado hasta la fecha con diferentes muestras: secreciones nasales y faríngeas, saliva, heces, ... pero en este trabajo en general, y en este punto en particular, nos centraremos en la técnica utilizada en sangre y LCR.

En nuestro entorno existen diferentes opciones para la identificación bacteriana en muestra sanguínea, siendo el test que identifica el meningococo, el neumococo y la *Listeria* el más utilizado. También se han comercializado test que tienen como objetivo la identificación bacteriana en LCR y que han provocado cambios en el manejo de estas infecciones. También es muy utilizado en la identificación de infecciones virales: enterovirus, herpesvirus, virus que afectan al sistema respiratorio, ... El mayor beneficio

de estos test es el ahorro de tiempo. Sin embargo, no todo son ventajas; no siempre están disponibles, cada test puede identificar un conjunto limitado de bacterias, son posibles los falsos positivos y por el momento tienen un coste importante.

Técnica basada en la reacción en cadena de la polimerasa (PCR)

Se trata de una técnica microbiológica que básicamente tiene el poder de hacer millones de copias a partir de un fragmento de ADN y se basa en la amplificación de determinadas partes del genoma bacteriano. La PCR ha supuesto un gran avance entre las técnicas de diagnóstico en la práctica clínica.

Ofrece algunas ventajas respecto a otras técnicas. Por un lado, los resultados están disponibles en un periodo muy corto de tiempo. Siempre bajo algoritmos de manejo sólidos y adecuados, abren el camino a decisiones más rápidas a pie de la cabecera del paciente. Las diferentes pruebas ofrecen diferentes sensibilidades y especificidades; sin embargo, en comparación con el cultivo, la sensibilidad, de manera general, es mayor con estas nuevas técnicas. Aún así, por el momento, no se ha recomendado sustituir el cultivo por la PCR en el algoritmo diagnóstico de las IBI[121,122].

Por otro lado, el hecho de que el antibiótico se haya administrado antes de la toma de la muestra, tiene un impacto menor en la capacidad de identificación bacteriana, en comparación con el cultivo. Para la identificación de *N. meningitidis*, la sensibilidad de las técnicas PCR ronda el 95% para las muestras obtenidas en el LCR y algo más baja para las muestras de sangre. Aunque el ADN meningocócico puede detectarse hasta 72 horas después del inicio de la antibioterapia sistémica, es recomendable ser prudente al interpretar los resultados negativos deducidos mediante esta técnica, ya que la presentación clínica, la gravedad, la duración y el momento de inicio del tratamiento antibiótico de la enfermedad podrían afectar al rendimiento[3,123,124].

En los últimos años se han lanzado al mercado otras opciones basadas en esta técnica, paneles que recogen una gran variedad de microorganismos, paneles múltiples FilmArray, que pueden ocupar un lugar preferente en algunos algoritmos. En comparación con los test habituales similares que son leídos a tiempo real, la amplificación y la lectura no se llevan a cabo simultáneamente, lo que supone que el test realiza una interpretación cualitativa de la presencia o ausencia de material genético del agente infeccioso. A pesar de las enormes ventajas que estos paneles ofrecen (los resultados los podemos tener en una hora por ejemplo en el caso del test FilmArray ® Panel meningitis-encefalitis), también tienen sus limitaciones: los resultados obtenidos son cualitativos; el panel sólo deduce la presencia de la lista de los microorganismos que ofrece; los resultados fuera de algoritmos de trabajo estrictos bien estudiados pueden tener interpretaciones difíciles (interpretación por ejemplo de la presencia positiva de los virus de la familia herpes virus, por su capacidad de integración en el genoma humano).

Técnicas de imagen

Algunas técnicas de imagen pueden ser útiles cuando estamos atendiendo a un paciente con fiebre en el servicio de urgencias. Por ejemplo, ante el paciente sospechoso de infección osteoarticular, la primera prueba de imagen recomendada por las guías suele ser la radiografía[75,125].

Sin embargo, los cuadros clínicos bajo sospecha de infección osteoarticular que se consultan en nuestro entorno suelen ser cuadros poco evolucionados y lo normal es que las características radiológicas significativas aún no fueran visibles y que este test no provocara cambios de decisión en el manejo terapéutico. La ecografía musculoesquelética puede ocupar su lugar en los cuadros clínicos con sospecha de artritis séptica para deducir la presencia o no de líquido en la articulación y ayudar en las técnicas de drenaje[126].

En pacientes febriles con dificultad respiratoria la neumonía puede ser uno de las causas. La mayoría de las guías no consideran del todo obligatoria la necesidad de imagen radiológica para aplicar el diagnóstico de neumonía a un determinado paciente, a pesar de ser una práctica habitual en los países desarrollados y sobre todo en los centros donde este recurso está disponible día y noche. Existen, sin embargo, determinadas indicaciones que sugieren realizar una radiografía[55,127]. En los últimos años también ha ocupado un lugar importante la ecografía pulmonar que se realiza a la cabecera del paciente, realizada por el médico no radiólogo, y que está teniendo resultados aceptables. Sin embargo, la evidencia científica todavía no es completa; entre sus limitaciones, la variabilidad entre los profesionales es la más importante, en relación con la experiencia del explorador[128].

Protocolos

Son las herramientas necesarias que facilitan que cualquier sistema funcione con seguridad. En el caso de un servicio de urgencias pediátrico, debe tratarse de estrategias diagnóstico-terapéuticas basadas en la evidencia científica y adaptadas a los recursos locales.

Los protocolos diseñados para diferentes cuadros clínicos van dirigidos a disminuir la variabilidad en la práctica clínica de los profesionales, garantizando en gran medida el beneficio clínico, económico y la seguridad del paciente.

En los siguientes puntos nos ocuparemos de la explicación de los diferentes protocolos clínicos.

Pacientes previamente no sanos

Cada vez es más frecuente atender a pacientes con patología crónica en un servicio de urgencias. La calidad de vida y la esperanza de los pacientes crónicos ha aumentado en

las últimas décadas. A medida que avanza la evidencia científica diferentes sociedades han realizado adaptaciones en los algoritmos de diagnóstico y tratamiento de pacientes con mayor riesgo de sufrir una infección bacteriana grave.

En pacientes portadores de dispositivos, como válvulas de derivación ventrículo-peritoneal o similares, catéter central o reservorio, o con dispositivos necesarios para realizar hemodiálisis, … la aproximación diagnóstica debe ser diferente. En los últimos años también se han ido modificando los procedimientos en pacientes oncológicos y/o inmunodeprimidos, se ha individualizado el manejo de los pacientes crónicos, se ha establecido un manejo más conservador en pacientes pediátricos con malformaciones complejas de las vías urinarias, y un largo etcétera. El objetivo de esta tesis no es explicar uno a uno los protocolos de cada grupo de riesgo y, además, desde el artículo que marca el inicio de esta tesis hasta el último, los diferentes protocolos han sido actualizados y los pacientes han ido recibiendo un manejo cada vez más personalizado.

Pacientes previamente sanos

Definiremos al resto de pacientes como pacientes previamente sanos. Estos, en general, tendrán menos riesgo de sufrir infecciones más graves. Por ello, la aproximación al estudio de estos pacientes debe ser sistematizada y equilibrada.

Ante un paciente con fiebre o con sospecha de infección, el paso más importante que debe dar el médico es decidir si este paciente debe recibir algún tratamiento de forma precoz, es decir, si está grave o no; si está estable o no; para ello se utilizan diferentes escalas y herramientas de decisión como el TEP, ya previamente comentado[62]. La mayoría de los pacientes que son atendidos con fiebre llegan estables al servicio de urgencias. Una vez objetivada la estabilidad del paciente, la siguiente decisión importante será diferenciar entre la fiebre con o sin aparente focalidad.

La anamnesis y la exploración física pueden explicar el origen de la fiebre y conducirán al médico a decidir solicitar pruebas complementarias, especialmente para determinar si requiere o no un tratamiento antibiótico. En el caso de una infección de las vías respiratorias superiores, si el examen físico revela una zona de hipoventilación pulmonar, puede sospechar neumonía y decidir en cada caso si solicitar alguna prueba de imagen, previa a iniciar el tratamiento. Por otro lado, la recomendación más frecuente, en ausencia de indicios de focalidad tras la exploración física, suele ser la de continuar con el tratamiento sintomático[55,127], aun sabiendo que dentro de este grupo de pacientes puede haber alguno que sufra una IBI.

Si a la fiebre se le añaden síntomas relacionados con las vías urinarias, se realizarán pruebas que puedan determinar una infección urinaria; la tira reactiva y en el caso de que esté alterada, el cultivo de orina. En el caso de infecciones de piel y tejidos blandos o infecciones osteoarticulares u otorrinolaringológicas, el examen físico proporcionará una gran información sobre la necesidad o no de realizar pruebas complementarias y, en su caso, establecer un tratamiento antibiótico ambulatorio o intravenoso.

En los casos de sospecha de meningitis, el paciente puede mostrar un triángulo pediátrico estable, aunque esto no es lo más frecuente. El objetivo principal es identificar al niño que sufre meningitis y deducir si el origen de la meningitis es viral o bacteriano. La administración precoz de antibiótico ante una meningitis bacteriana supone una mejora del pronóstico. Por otro lado, la identificación de la meningitis viral evitará estancias innecesarias de hospitalización y tratamiento, junto con la iatrogenia que genera. Sin embargo, esta identificación no es nada sencilla, ya que la ausencia de signos patognomónicos y la consulta precoz de los pacientes condiciona que los signos y síntomas sean inespecíficos. El diagnóstico se sustentará en el resultado del análisis y el

cultivo del LCR, que es la clave. Sin embargo, el resultado del cultivo no es inmediato y en los últimos años se han llevado a cabo varios intentos para aumentar la precisión de este proceso diagnóstico, publicándose varios score o reglas de predicción clínica y guías de diagnóstico, con el fin de reducir esta incertidumbre[129,130]. Estos scores combinan datos clínicos y también analíticos (sangre y LCR).

Por último, la aparición de técnicas microbiológicas basadas en la reacción en cadena de polimerasa ha facilitado, sobre todo, la toma de decisiones más tempranas al incluirse en el proceso diagnóstico.

Las infecciones bacterianas más graves, como ya se ha mencionado en la introducción de la tesis, son las causadas por bacterias que se aíslan en sangre o LCR. La bacteriemia oculta, aunque no sea la infección bacteriana invasiva más grave, es un cuadro clínico relativamente frecuente. La bacteriemia oculta se define cuando se aísla una bacteria en la sangre de un paciente con fiebre, con triángulo pediátrico estable, en el que los síntomas y el examen físico no pueden explicar el origen de la fiebre.

Un grupo de pacientes en el que se han realizado esfuerzos muy intensos en la búsqueda activa de bacteriemia oculta, es el de los lactantes menores de 3 meses de edad, previamente sanos. En esta edad, los agentes más frecuentes son el *E. coli* y el estreptococo del grupo B. La inmadurez del sistema inmunitario y el hecho de que el programa de vacunación no haya comenzado, les hacen entre otras razones, ser susceptibles de sufrir una infección bacteriana grave. Sin embargo, muchos de estos niños son actualmente candidatos a un seguimiento ambulatorio sin antibióticos. Han sido muchas las estrategias propuestas para conseguirlo, desde los criterios de Rochester, Philadelphia y Boston hasta la actualidad, pero las tasas de adhesión que se han alcanzado a estas guías de actuación no han sido muy elevadas[131]. Los nuevos biomarcadores que

han aparecido en los últimos años y el resultado del trabajo llevado a cabo a lo largo en las últimas décadas, han conseguido un manejo menos intervencionista de los lactantes más pequeños. En nuestro entorno, "Step by Step" y la norma PECARN son las herramientas más utilizadas en el manejo de estos pacientes[132,133,134]. No obstante, estas herramientas no son estrategias fijas y han experimentado cambios significativos con el tiempo y las evidencias emergentes.

Otro grupo de pacientes que se ha investigado con intensidad es el de los lactantes febriles previamente sanos de 3 a 24 meses de edad. Históricamente, *S. pneumoniae* fue la bacteria más frecuentemente aislada, pero las complicaciones más severas (tasas de meningitis, secuelas graves y mortalidad) eran las provocadas por *H. influenzae*[135]. Desde la universalización de las vacunas frente a *H. influenzae*, la tasa de bacteriemia oculta disminuyó considerablemente[136]. Las vacunas conjugadas frente al neumococo que se han universalizado en los últimos años también han supuesto un descenso significativo de las infecciones invasivas neumocócicas. La aparición de la vacuna conjugada antineumocócica heptavalente cursó principalmente con el descenso de la bacteriemia oculta neumocócica[3,7,8].

Esta tendencia fue similar tras la introducción de la vacuna conjugada trecevalente a partir del año 2010 y algunas series indicaron que el neumococo no sería la bacteria más frecuentemente aislada[64,137,138].

Según el artículo clásico de Lee, la realización de test sanguíneos que pueden indicar la presencia de una bacteriemia oculta en un paciente con fiebre sin focalidad, está justificada cuando la prevalencia de la enfermedad supera el 1,5%, siendo además coste-efectiva[5,11]. Por el contrario, cuando la tasa está por debajo del 0,5%, no hay recomendación para la realización sistemática de test en sangre.

Debido a que la prevalencia de bacteriemia oculta neumocócica en la actualidad es baja, hay guías que ya no recomiendan realizar análisis de sangre de manera sistemática a los lactantes febriles, con buen estado general y bien vacunados (al menos dos dosis de vacuna conjugada frente al neumococo)[139]. De hecho, según estudios actuales, la tasa de bacteriemia oculta es muy baja en la población correctamente vacunada[140].

Si se cree estar ante una sepsis, se implementarán todos los esfuerzos dirigidos a la estabilización del paciente. En general, el triángulo pediátrico no será estable, por lo que la monitorización será imprescindible. Se tomarán todas las medidas disponibles para asegurar el mantenimiento de la vía aérea y la oxigenación y ventilación más adecuadas, tanto por técnicas de ventilación invasiva como no invasiva. Se realizarán los cuidados imprescindibles para mantener la perfusión de los órganos y se priorizarán las terapias de sueroterapia y drogas vasoactivas para conseguir un gasto cardiaco y tensión adecuados. La antibioterapia, será de amplio espectro y las guías más recientes recomiendan implantarla en las tres primeras horas en el caso de la sepsis y dentro de la primera hora en el caso del shock séptico.

CAMBIOS EN LAS ÚLTIMAS DÉCADAS

Cambios sociales

Los cambios socioculturales experimentados por las sociedades occidentales en las últimas décadas (menor número de hijos e hijas, acceso de las mujeres al mercado laboral, mayor y más fácil acceso a la información) han tenido un claro impacto en los servicios sanitarios que se ofrecen. De esta forma, en el caso del niño con fiebre, las familias acuden con mayor frecuencia y, sobre todo, con mayor rapidez al médico, bien a su médico habitual u otro que pueda estar disponible y genere confianza y también a los servicios de urgencias hospitalarias[141]. Así, en la actualidad, en las sociedades occidentales, incluida la vasca, la fiebre es uno de los motivos más frecuentes de consulta en los servicios de urgencias de pediatría hospitalaria. Además, en nuestro entorno, las familias suelen consultar muy rápido. En los últimos años, los servicios de emergencia han experimentado un notable aumento de las consultas registradas[142,143]. Este fenómeno ha sido explicado por diversas sociedades occidentales, también en el País Vasco[141].

Este aumento de consultas en los servicios de emergencias ha obligado a estos dispositivos a adecuar sus recursos a la demanda actual desde el punto de vista arquitectónico, personal y organizativo. Sin embargo, a menudo estos servicios sufren situaciones cercanas a la saturación y dificultan el día a día de los profesionales que trabajan en ellos[144,145].

Por otro lado, se sabe que, en nuestro entorno los tiempos de evolución de los cuadros clínico suelen ser muy recortados. Por ejemplo, en el caso del lactante menor de 3 meses de edad con fiebre sin focalidad, la mediana de la duración de la fiebre hasta la consulta

fue de dos horas[146] en una serie de pacientes reclutados en los últimos cinco años. Esto dificulta la identificación de pacientes con IBI.

Cambios en sanidad

En las últimas décadas se han producido importantes avances en el ámbito de la salud como en cualquier otro ámbito, sobre todo a partir de los avances de la tecnología. Todos estos cambios afectarán a la gestión que desde el servicio de urgencias realizamos en colaboración con la familia de los niños que consultan por un proceso febril.

Ecografía prenatal

La universalización de la ecografía prenatal ha facilitado el diagnóstico prenatal de muchas de las importantes malformaciones que puede sufrir un recién nacido.

Las anomalías más frecuentes son las relacionadas con el riñón y el aparato urinario[147,148]. Entre ellas, la anomalía más frecuente es la hidronefrosis, con una incidencia del 0,5-1%[149,150]. Aunque no todos los niños en los que se detecta hidronefrosis prenatal sufrirán posteriormente patologías relacionadas con las vías urinarias, un porcentaje significativo de este grupo de pacientes puede presentar una lesión que le provoque alteraciones pieloureterales importantes[151] y, según otros autores, el 35% de este grupo de pacientes puede presentar reflujo vesicoureteral[152]. Clásicamente, las malformaciones más evidentes se podían sospechar en la primera exploración física rutinaria del recién nacido, sobre todo ayudado por la palpación renal o a raíz de signos y síntomas derivados de la insuficiencia renal. No obstante, en la mayoría de los casos, el diagnóstico se sospechaba al diagnosticar una infección urinaria en un lactante que consultaba con fiebre sin focalidad y realizar el subsiguiente estudio. Actualmente, gracias a la ecografía prenatal, el pediatra tiene la capacidad de conocer gran parte del grupo de niños con riesgo de sufrir una infección urinaria. Por ello, el proceso de estudio de estos pacientes será diferente.

Detección del estreptococo del grupo B en mujeres embarazadas

El estreptococo del grupo B o *Streptococcus agalactiae* fue declarada la principal causa de sepsis neonatal y meningitis en la década de 1970[153].

Otros autores lo han relacionado posteriormente con tasas muy destacadas de meningitis (39%), otras infecciones focales (10%) y sepsis (7%)[154]. En los últimos años, el uso de profilaxis antibiótica intraparto ha reducido la incidencia de infecciones por este germen[155,156,157].

Esta profilaxis ha reducido sobre todo las infecciones precoces, aunque no se ha descrito una reducción paralela de infecciones tardías por el estreptococo del grupo B[158,159,160].

Según algunos estudios, la incidencia de la enfermedad por estreptococo del grupo B de Estados Unidos ha disminuido de 1,8 casos por 1.000 nacimientos en 1990 a 0,32 por 1.000 en 2003[161,162]. La mortalidad global de la enfermedad precoz causada por *Streptococcus* de grupo B, ha pasado del 50% registrado en la década de los 70 al 5-6% detectado entre 1993 y 2003, gracias principalmente a los mecanismos de atención y cuidados que se prestan al recién nacido[160,163]. La búsqueda sistemática de la bacteria que se realiza en el tercer trimestre del embarazo de las mujeres y las decisiones que se toman en función de este resultado (tratamiento antibiótico que se administra en el trabajo de parto) ha reducido la incidencia de recién nacidos infectados por el estreptococo del grupo B[164,165]. En los últimos años podemos afirmar que esta bacteria no es la bacteria más común que se aísla en infecciones invasivas en pacientes menores de 3 meses con fiebre sin foco en nuestro entorno[23,166]. De cara al futuro, la instauración y el impacto que puedan tener las vacunas frente al estreptococo del grupo B son esperanzadoras.

Calendario vacunal

A nivel mundial y tras el procedimiento de potabilización del agua, el avance que más ha disminuido históricamente el riesgo de infección ha sido la implantación del calendario vacunal.

La vacunación sistemática rebaja mucho la probabilidad de sufrir infecciones graves. Las campañas de vacunación de los últimos años han supuesto una reducción de las sepsis y meningitis, con la consiguiente reducción de daños colaterales y secuelas de larga duración y muerte. En este capítulo de esta tesis nos centraremos en la vacunación conjugada contra *Haemophilus influenzae*, meningococo y neumococo, que son las vacunas que más han influido en los IBI de nuestro entorno.

Vacuna frente a *Haemophilus influenzae* B

La vacunación universal frente a *H. influenzae* de tipo B ha eliminado casi por completo las enfermedades invasivas causadas por esta bacteria[167]. De hecho, hoy en día es excepcional que un niño correctamente vacunado sufra una infección invasiva por *H. influenzae* de tipo B[168]. En la era prevacunal, la gran mayoría de los casos de infecciones invasivas por *H. influenzae* de tipo B (más del 80%) se detectaban en niños menores de cinco años y sobre todo en menores de dos años[167]. Esta bacteria fue una de las principales responsables de bacteriemias ocultas, pero también causante de la mayoría de las complicaciones. De hecho, alrededor de un 10-20% de estas bacteriemias provocaban posteriormente una meningitis[169]. Debido a la suma de la protección directa e indirecta provocada por la universalización de esta vacuna, el manejo del niño atendido con fiebre sin foco en urgencias varió ya que acarreó una disminución casi total de la enfermedad[170,171,172,173,174,175].

Vacunas frente a *Neisseria meningitidis*

El meningococo es una bacteria que produce ondas epidémicas. En la década de 1980 a 1990 se produjo un notable aumento de las enfermedades meningocócicas. Es cierto que este aumento puede explicarse en parte por la mejora de las técnicas diagnósticas basadas en la PCR[176,177].

En cualquier caso, en aquellos años los casos de enfermedad meningocócica por serogrupo C aumentaron de forma importante en varios países europeos, como Inglaterra y Gales[178,179], Grecia[180] o España[181]). Este aumento también fue notificado en Canadá[182]. El incremento fue más importante entre estos dos grupos de edad, los menores de 2 años y los de 15 a 19 años. El descenso de las enfermedades invasivas causadas por *H. influenzae B* también es aplicable al meningococo C gracias a la incorporación de una vacuna específica[183]. De hecho, esta disminución se puede explicar por la campaña de vacunación iniciada en el año 2000. Su efectividad se ha comprobado año tras año. Así, la incidencia de infecciones invasivas por serogrupo C disminuyó drásticamente, con 0,04 casos/100.000 habitantes en la temporada 2014-2015[184,185].

No obstante, en nuestro entorno, el serogrupo B ha sido el más prevalente de todos, exceptuando esta importante onda provocada por el serogrupo C de la década de los 90. La incidencia global de infecciones por *Neisseria meningitidis* ha tenido además una tendencia a la baja en España desde el año 2000. La tasa de incidencia más baja de casos confirmados se situó en el periodo 2013-2014 en torno a 0,5 casos por 100.000 habitantes. Sin embargo, más de la mitad de los casos siguieron siendo provocados por el serogrupo B. Este descenso comenzó hace dos décadas y puede estar en parte explicado por el patrón periódico que ofrece la propia enfermedad, ya que la vacuna conjugada frente al serogrupo B no parece que haya podido tener un impacto tan significativo por el

momento; la comercialización comenzó en octubre de 2015 y además, no forma parte de las campañas de vacunación de todas las comunidades autónomas[65,185].

A partir del año 2015, la cifra aumentó ligeramente, alcanzando una tasa de incidencia de 0,83 casos[67] por 100000 habitantes, debido principalmente al aumento del serogrupo W135. Varios expertos llegaron a afirmar que estábamos ante una nueva onda epidémica del meningococo.

Vacuna frente a *Streptococcus pneumoniae*

Aunque la vacuna que ofrecía la protección frente a 23 serotipos ya estuviera disponible desde 1977, no era efectiva en niños menores de 2 años debido a la falta de madurez que ofrece el sistema inmunitario a esta edad.

En el año 2000 se aprobó la vacuna conjugada heptavalente (PCV7) formada por polisacáridos de siete variantes de *S. pneumoniae* (4, 6B, 9V, 14, 18C, 19F y 23F). Primero en Estados Unidos y posteriormente, progresivamente, se adhirió a los programas de inmunización de la Unión Europea. Esta vacuna habría ofrecido una cobertura superior al 80% de las infecciones invasivas neumocócicas detectadas en Estados Unidos en el año 2000[33,186,187]. Desde la comercialización de esta vacuna, la incidencia global de infecciones invasivas por *Streptococcus pneumoniae* ha descendido considerablemente en todos los grupos de edad, pero especialmente en niños menores de dos años, incluso en no vacunados[31,183,188].

Por otro lado, aunque se vivió una vacunación casi universal con la PCV7v, nuevos estudios e informes de diferentes redes de vigilancia y monitorización describieron un aumento de las infecciones por serotipos fuera de la cobertura que ofrecían las vacunas: principalmente las causadas por el serotipo 1, 19A, 7F, 3 y 6A; es la denominada "sustitución de serotipos". Además, el serotipo 19A, capaz de copar el 80% de las

multiresistencias antimicrobianas, se convirtió en una importante causa de infecciones invasivas desde la introducción de la vacuna conjugada heptavalente[6,183,188,189]. En 2010, la vacuna conjugada 13valente sustituyó a la PCV7v en los programas de vacunación de Estados Unidos. Esta vacuna recogió serotipos que provocaban la "sustitución de serotipos" que se produjo en años anteriores, entre ellos el 19A y el 7F. Una publicación actualizada del Centro de Control y Prevención de Enfermedades (CDC)[190], concluyó que este cambio de vacuna habría provocado una reducción del 64% de las infecciones invasivas por *Streptococcus pneumoniae* en niños menores de 5 años y una reducción del 93% de las IBI por nuevos serotipos incluidos en la vacuna 13valente [191,192,193,194]. La incidencia de IBI por serotipos integrados en la vacuna 13valente en pacientes de entre cinco y 15 años disminuyó un 75%. En general, tuvo el mismo efecto en todos los grupos de edad, debido principalmente al declive de los serotipos 19A y 7F[194,195]. Todo esto ha cambiado el manejo de un lactante con fiebre. Próximamente, dos "nuevos" serotipos responsables de gran parte de las IBI neumocócicas actuales podrían estar a punto de entrar en los calendarios de vacunación[196]. Esto también incide en la importancia de mantener una estrecha monitorización de las IBI.

HIPÓTESIS DE TRABAJO

En la actualidad, el paciente con IBI suele acudir en estadios muy precoces a los servicios de urgencias, cuando los síntomas y los signos que presentan en la anamnesis y en el examen físico pueden ser inespecíficos. La mayoría de estos pacientes son pequeños, lo que facilita que los signos y síntomas clásicos de las diferentes infecciones aparezcan en casos aislados. Las diferentes campañas de vacunación implantadas en los últimos años han cambiado las características epidemiológicas de los IBI. Todo esto ha podido dificultar la aproximación del médico a los pacientes con fiebre.

Por otra parte, los avances en la identificación del paciente febril con mayor riesgo de sufrir una IBI, debido al avance tecnológico y la disponibilidad de análisis más avanzados, han incrementado el número de pruebas que se pueden realizar en estos pacientes. Son muchas las características que influirán en el rendimiento de estas pruebas, máxime si los pacientes a los que se van a realizar no han sido previamente seleccionados.

En definitiva, las IBI siguen constituyendo un grave problema y un reto para el pediatra de urgencias. Uno de los principales retos será identificar la posibilidad de que el paciente febril que está estable pueda padecer una IBI, combinando la anamnesis, la exploración física y utilizando los diferentes test y pruebas complementarias cuando lo considere necesario.

Nuestra principal hipótesis es que la caracterización del paciente que sufre IBI y el rendimiento de los recursos disponibles para su identificación han podido sufrir variaciones en los últimos años. Este conjunto de recursos incluye anamnesis, exploración física y pruebas complementarias que podemos realizar en un servicio de urgencias.

OBJETIVOS PRINCIPALES

1. Caracterizar la presentación clínica de las IBI confirmadas en pacientes menores de catorce años.

2. Describir la gravedad de las IBI en pacientes menores de catorce años.

3. Analizar el valor de los test sanguíneos habituales (recuento leucocitario, número absoluto de neutrófilos, proteína C reactiva y procalcitonina) que se realizan para la identificación de IBI en pacientes menores de catorce años.

4. Evaluar la indicación de los test en sangre, en el manejo de niños de 3 a 24 meses de edad con fiebre sin focalidad y estabilidad clínica.

5. Describir la presentación clínica de las infecciones invasivas por *E. Coli* y analizar posibles perfiles y su posible relación con la gravedad.

6. Describir la presentación clínica de la infección invasiva por estreptococo del grupo B y analizar su posible relación con su gravedad.

OBJETIVOS SECUNDARIOS

Aunque no era objetivo de esta tesis, describir el impacto de una pandemia no esperada en la epidemiología de las IBI identificadas en un servicio de urgencias pediátrico.

MÉTODO

ARTÍCULOS PUBLICADOS E ÍNDICES DE CALIDAD

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Characteristics of children with microbiologically confirmed invasive bacterial infections in the emergency department

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Background **Determination of the characteristics of paediatric invasive bacterial infections (IBI) is essential for early identification of children requiring immediate antibiotic therapy. The main objective is to characterize the emergency presentation of the IBI among children aged younger than 14 years.**

Patients and methods **A prospective registry-based cohort study including all patients aged younger than 14 years diagnosed with confirmed IBI (culture or genomic detection using the polymerase chain reaction) was carried out in a paediatric emergency department between 2008 and 2015. Severity criteria were as follows: death, sequelae or admission to the ICU.**

Results **Of the 223 IBIs reported, 187 (83.9%) corresponded to previously healthy patients (median age = 19 months) and 165 (74%) were well appearing. The most common diagnoses were occult bacteraemia [60 (26.9%)] and sepsis [56 (25.1%)]. The most frequent pathogens were *Streptococcus pneumoniae* [68 (30.5%)] and *Neisseria meningitidis* [42 (18.8%)]. Four (1.8) patients died (*S. pneumoniae*, 2) and eight (3.5%) had sequelae (*S. pneumoniae*, 5). The diagnoses and clinical characteristics of the children varied significantly depending on the isolated pathogen. Duration of fever less than 24 h, symptoms other than fever and not being well-appearing upon arrival to the emergency department were independent risk factors for greater severity (area under the receiver operating characteristics curve = 0.805; 95% confidence interval: 0.741–0.868).**

Conclusion **IBIs are commonly diagnosed in previously healthy and well-appearing young children. *S. pneumoniae* was responsible for the majority of deaths or sequelae. Short duration of fever, symptoms other than fever and not being stable on arrival are associated with greater severity. *European Journal of Emergency Medicine* 00:000–000**

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Keywords: invasive bacterial infection, meningitis, occult bacteraemia, sepsis

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Introduction

Fever is a very common reason for consultation among children attending the emergency department (ED) [1]. In most cases, the cause is a self-limiting viral infection. Despite advances in vaccinations and antibiotics, meningitis and sepsis remain significant causes of death of children in developed countries. Early identification of these children is essential to initiate immediate antibiotic therapy. In fact, early recognition and treatment of children with an invasive bacterial infection (IBI) is an imperative for emergency physicians. Nevertheless, identification of patients with an IBI may be difficult. Nowadays, patients with an IBI are often brought to the ED after only a few hours of fever, the signs and symptoms often being difficult to differentiate from benign self-limited febrile illnesses [2]. In addition, most of these patients are younger than 2–3 years of age, at which the manifestations of the different infectious diseases are usually more nonspecific [3].

However, the microorganisms causing the IBIs have changed over the last decades, mostly because of the vaccines developed against the microorganisms responsible for most of them. Thus, the implementation of the *Haemophilus influenzae* b (Hib) conjugate vaccine led to the virtual eradication of this microorganism in vaccinated populations [4]. Subsequent implementation of the routine vaccination policy with pneumococcal conjugate vaccines (PCV, both seven-valent PCV and 13-valent PCV) led to a marked decrease in invasive pneumococcal diseases [5]. Furthermore, meningococcal C conjugate vaccination also significantly decreased the invasive meningococcal infections [6].

Despite the importance of knowing both the clinical and the microbiological characteristics of paediatric patients

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with an IBI, there are no large recent studies published in Europe.

The main objective is to characterize the emergency presentations of IBI among children aged younger than 14 years and their main profiles.

The secondary objective is to identify factors related to a greater severity.

Patients and methods

We carried out a prospective registry-based cohort study that included all the patients aged younger than 14 years diagnosed with an IBI in a paediatric ED between January 2008 and December 2015. Our ED is a tertiary teaching hospital and, each year, receives around 55 000 children younger than 14 years of age.

The results for the first 2 years of this registry were used to describe patients diagnosed with an IBI after the introduction of the PCV7 in Spain [2].

During the period of the study, all patients younger than 14 years of age attending the ED and diagnosed with IBI were identified using the electronic records of our hospital. Each month, a report with all the cultures obtained in the ED was sent by one of the investigators (M.S.) from the Microbiology Service to other ED investigator (S.M.), who identified all the patients with a bacterial pathogen in blood and/or cerebrospinal fluid (CSF) by growth in bacterial culture and/or genomic detection of *Neisseria meningitidis* and *Streptococcus pneumoniae* using the PCR. These episodes were revised by two other investigators (I.G., J.V.) and disagreements were resolved with consensus from a third investigator (S.M.). Information on the patient and the episode was obtained from the electronic clinical records of the paediatric ED and the public health system.

The following data were collected: age, sex, personal history, month and year of consultation, pneumococcal vaccination status, duration of fever, associated symptoms, maximum temperature, previous consultation in the ED, appearance upon arrival, physical exam, microorganism isolated, final diagnosis, destination and evolution of the patient (Supplementary Table 1, Supplemental digital content 1, *http://links.lww.com/EJEM/A157*).

Definitions

(1) IBI: identification of bacterial pathogen in blood and/or CSF by growth in bacterial culture and/or genomic detection of *N. meningitidis* and *S. pneumoniae* using the PCR technique (RealCycler MENE and RealCycler MENELI; Progenie Molecular, Valencia, Spain). Patients with a blood culture in which a bacterial species classically considered a contaminant was isolated (including *Staphylococcus epidermidis*, *Propionibacterium acnes*, *Streptococcus viridans*, *Corynebacterium* spp., and other diphtheroids) were excluded if the samples were collected in otherwise healthy patients. In these immunocompromised children, a definitive diagnosis of catheter-related bloodstream infection required positive percutaneous blood culture results with concordant microbial growth from the catheter tip or catheter-drawn cultures
(2) Previously healthy patient: patients without any of the following risk factors: (a) immunosuppression (oncological illness, chronic renal failure, transplant patient, sickle cell disease); (b) the presence of a mechanical device (indwelling catheter, ventriculoperitoneal shunt, auditory prostheses); and (c) an invasive diagnostic or therapeutic procedure in the previous 10 days.
(3) Well-appearing patients: patients with a stable paediatric assessment triangle upon arrival at the ED [7].
(4) Occult bacteraemia: isolation of pathogenic bacterium in the blood of a well-appearing child with fever without a source (absence of signs of a focal infection).
(5) Sepsis: life-threatening organic dysfunction because of a dysregulated host response to infection [8].
(6) Septic shock: those patients with persisting hypotension requiring vasopressors despite adequate volume resuscitation.
(7) Severity criteria: the following were considered:
    (a) Death.
    (b) Sequelae.
    (c) Admission to the Paediatric ICU (PICU).

The study was approved by the Clinical Research Ethics Committee of the hospital. To maintain patient confidentiality, the database did not include any data that would have allowed the identification of patients. As identities remained anonymous and no intervention was performed on patients, informed consent was not required.

Statistical analysis

The qualitative variables were described using absolute frequencies and percentages and the continuous variables were described using either the mean and SD or median and interquartile range. The χ^2-test was used to study the association between qualitative variables. Poisson regression models were used to analyse incidence rates of pneumococcal IBI for time period.

A multivariate binary logistic regression was performed to identify the independent risk factors related to a greater severity of the process. Death, sequelae and/or admission to the PICU were used as severity criteria. In this way, the outcome measure was the presence of, at least, one of the following: death, sequelae and admission to PICU. A univariate logistic regression analysis was carried out

initially. All variables with P less than 0.2 were subsequently included in a nonautomatic multivariate stepwise model. All variables with P less than 0.05 were included in the final multivariate model. The results of the model are presented as odds ratio and 95% confidence interval (CI). The area under the receiver operating characteristics curve was calculated for the final model. The goodness of fit of the model was evaluated using the Hosmer–Lemeshow test.

All statistical analyses were carried out using the SPSS statistical software package, version 23.0 (IBM, Armonk, New York, USA).

Results

During the study period, 456 830 episodes corresponding to children aged younger than 14 years were registered in the ED. Of these, 223 were diagnosed with an IBI (0.048%, 95% CI: 0.047–0.049) by growth in bacterial culture and/or genomic detection of *N. meningitidis* and *S. pneumoniae* using the PCR. Globally, 187 (83.9%) were previously healthy; there was a slight predominance of males [126 (56.5%)] and the median age was 19 months (interquartile range: 5 months to 2 years). Almost 50% [102 (45.7%)] came to the ED between October and January. The global characteristics of those patients diagnosed with an IBI are shown in Table 1.

S. pneumoniae [68 (30.5%)] and *N. meningitidis* [42 (18.8%), Table 2] accounted for nearly 50% of the IBIs. The rate of pneumococcal IBI changed before and after the implementation of the routine vaccination policy with PCV13 (Fig. 1). A decreasing trend was found for pneumococcal IBI in the period 2008–2015; this was not statistically significant [Incidence rate ratio = 0.911 (95% CI: 0.820–1.013); $P = 0.085$]. *S. pneumoniae* was serotyped in 57 patients, 37 (64.9%) of whom were included in the PCV13.

The final diagnoses, age and clinical characteristics of the patients varied significantly in terms of the isolated bacterial pathogen (Tables 3 and 4).

A total of 147 (65.9%) patients were admitted to hospital (64 in the PICU, 28.7% of all patients).

The vast majority [218 (97.8%)] did well, although four (1.8%) died (28-day mortality) and eight (3.6%) had sequelae (Table 5). Three children with a ventriculoperitoneal shunt experienced a shunt failure, requiring a replacement.

Presenting to the ED during the first 24 h of the disease, the presence of symptoms other than fever and not appearing well upon arrival at the ED were independent risk factors for greater severity (Table 6). This model showed an area under the receiver operating characteristics curve of 0.805 (95% CI: 0.741–0.868) and the P value of the Hosmer–Lemeshow test was 0.356.

Table 1 Characteristics of the patients diagnosed with an invasive bacterial infection

	n (%)	95% CI
Sex (male)	126 (56.5)	50–63
Age: < 12 months	86 (38.6)	32.2–45
Increased risk of invasive bacterial infection		
No	187 (83.8)	78.9–88.6
Immunological and/or with central venous catheter	21 (9.5)	5.6–13.3
Others	15 (6.7)	3.4–9.9
Pneumococcal vaccine dose received		
Unknown	24 (10.8)	6.7–14.8
None	117 (52.5)	45.9–59
1 doses	9 (4)	1.4–6.5
2 doses	13 (5.8)	2.7–8.8
3 doses	29 (13)	8.5–17.4
4 doses	31 (13.9)	9.3–18.4
Duration of fever		
Afebrile	8 (3.6)	1.1–6
< 6 h	64 (28.7)	22.7–34.6
6–24 h	63 (28.3)	22.3–34.2
> 24 h	88 (39.4)	33–45.8
Symptoms		
Fever only	64 (28.7)	22.7–34.6
Respiratory	44 (19.7)	14.5–24.9
Digestive	60 (26.9)	21.1–32.7
Neurological	35 (15.7)	10.9–20.5
Rash	21 (9.4)	5.5–13.2
Osteoarticular and/or soft tissue	19 (8.5)	4.8–12.1
Others	14 (6.3)	3.1–9.5
Well appearing upon arrival at the emergency department	165 (74)	68.2–79.7
Physical examination		
Normal	92 (41.3)	34.8–47.7
Rash	52 (23.3)	17.7–28.8
Abnormal pulmonary auscultation	28 (12.6)	8.2–16.9
Alteration of the central nervous system	32 (14.3)	9.7–18.9
Osteoarticular and/or soft tissue findings	15 (6.7)	3.4–9.9
Others	18 (8.1)	4.5–11.6

CI, confidence interval.

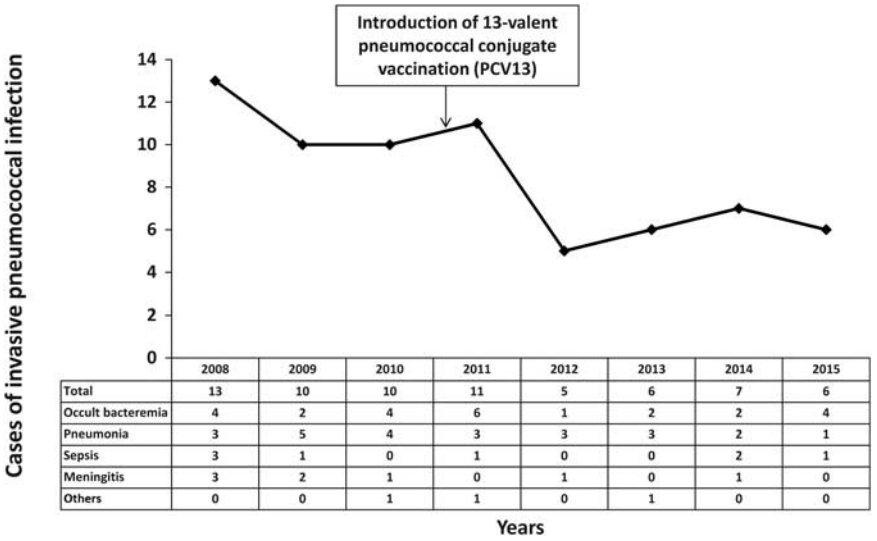
Table 2 Bacteria isolated from patients with an invasive bacterial infection

Bacteria	*n* (%)	95% CI
Streptococcus pneumoniae	68 (30.5)	24.5–36.5
Neisseria meningitidis	42 (18.8)	13.7–23.9
Escherichia coli	33 (14.8)	10.1–19.5
Staphylococcus aureus	25 (11.2)	7.1–15.3
Streptococcus agalactiae	9 (4)	1.4–6.6
Streptococcus pyogenes	9 (4)	1.4–6.6
Staphylococcus coagulase (–)	8 (3.6)	1.1–6.1
Enterococcus faecalis	6 (2.7)	0.6–4.8
Others: 23 (*Salmonella* spp. 5, *Pseudomonas aeruginosa* 3, *Klebsiella* spp. 3, *Proteus mirabillis* 2, *Haemophilus influenzae* 2, *Listeria monocytogenes* 1, *Moraxella catharralis* 1, *Morganella morgagni* 1, *Propionebacterium acnes* 1; *Streptococcus mitis* 1, *Staphylococcus lugdunensis* 1, *Streptococcus salivarius* 1; *Campylobacter jejuni* 1)	23 (10.3)	6.4–14.4

Data are expressed as *n* (%) and 95% CI.
CI, confidence interval.

Meningococcal infections were the most severe IBI (odds ratio: 12.3, 95% CI: 5.3–28.4), as was also the case for patients diagnosed with sepsis or meningitis with respect to other diagnoses (82.1, 44.0 and 7.0%, respectively, $P < 0.001$).

Fig. 1



	2008	2009	2010	2011	2012	2013	2014	2015
Total	13	10	10	11	5	6	7	6
Occult bacteremia	4	2	4	6	1	2	2	4
Pneumonia	3	5	4	3	3	3	2	1
Sepsis	3	1	0	1	0	0	2	1
Meningitis	3	2	1	0	1	0	1	0
Others	0	0	1	1	0	1	0	0

Cases of invasive pneumococcal bacterial infection by year.

Table 3 Isolated bacteria related to the final diagnosis of the patients

	Occult bacteraemia	Sepsis/shock	Pneumonia	Urinary tract infection	Meningitis	Arthritis/ osteomyelitis	Cellulitis/ abscess	Others	Total
Streptococcus pneumoniae	25 (36.8) 25.3–48.26	8 (11.8) 4.1–19.5	24 (35.3) 23.9–46.7	0	8 (11.8) 4.1–19.5	0	0	3 (4.3) 0–9.3	68 (30.5) 24.5–36.5
Neisseria meningitidis	2 (4.8) 0–11.26	30 (71.4) 57.7–85.1	0	0	10 (23.8) 10.9–36.7	0	0	0	42 (18.9) 13.7–23.9
Escherichia coli	2 (6.1) 0–14.2	3 (9.1) 0–18.9	0	26 (78.8) 64.8–92.8	2 (6.1) 0–14.27	0	0	0	33 (14.8) 10.1–19.5
Staphylococcus aureus	8 (32.0) 13.7–50.3	1 (4.0) 0–11.7	1 (4.0) 0–11.7	1 (4.0) 0–11.7	0	13 (52.0) 32.4–71.6	0	1 (4.0) 0–11.7	25 (11.2) 7.1–15.3
Streptococcus agalactiae	2 (22.2) 0–49.4	6 (66.7) 35.9–97.5	0	0	1 (11.1) 0–31.6	0	0	0	9 (4) 1.4–6.6
Streptococcus pyogenes	3 (33.3) 2.5–64.1	2 (22.2) 0–49.4	1 (11.1) 0–31.6	0	0	0	3 (33.3) 2.5–64.1	0	9 (4) 1.4–6.6
Staphylococcus coagulase (–)	5 (62.5) 28.9–96.0	1 (12.5) 0–35.4	0	0	1 (12.5) 0–35.4	0	1 (12.5) 0–35.4	0	8 (3.6) 1.1–6.1
Enterococcus faecalis	4 (66.7) 29–100	0	1 (16.7) 0–46.5	0	1 (16.7) 0–46.5	0	0	0	6 (2.7) 0.6–4.8
Others	9 (39.1) 19.2–59	5 (21.7) 4.8–38.5	0	0	2 (8.7) 0–20.2	0	1 (4.3) 0–12.6	6 (26.1) 8.1–44.1	23 (10.3) 6.3–14.3
Total	60 (26.9) 21.1–32.7	56 (25.1) 19.4–30.8	27 (12.1) 7.8–16.4	27 (12.1) 7.8–16.4	25 (11.2) 7.1–15.3	13 (5.8) 2.7–8.9	5 (2.2) 0.3–4.1	10 (4.5) 1.8–7.2	223

Data are expressed as *n* (%) and 95% CI.
CI, confidence interval.

IBI was diagnosed at a second visit to the ED in 32 (14.3%) patients (13 *S. pneumoniae* and seven *N. meningitidis*). Of these, six were finally diagnosed with sepsis and one died. Four (12.5%) of these 32 patients died or presented sequelae [vs. eight (4.1%) of the 191 diagnosed at the first visit, $P=0.07$].

Discussion

This study shows that IBIs accounts for a very small percentage of children attending a paediatric ED, highlighting the scope of the challenge of identifying rare critical cases in a large population with universal access to a health care system. IBIs are often diagnosed in previously healthy well-appearing young children presenting early to the ED. Most of the children do well. Those children not well appearing, showing symptoms other than fever and attended to in the first 24 h of the fever had a worse outcome. The clinical characteristics, diagnoses and evolution of these patients varied depending on the bacterial pathogen isolated.

The most common isolated pathogen was *S. pneumoniae*, mainly responsible for the cases of occult bacteraemia and invasive pneumonia and, together with *N. meningitidis*, the

Table 4 Clinical characteristics of the invasive infections caused by the most common bacteria

	Streptococcus pneumoniae ($n=68$)[a]	*Neisseria meningitidis* ($n=42$)[b]	*Escherichia coli* ($n=33$)	*Staphylococcus aureus* ($n=25$)[c]	*Streptococcus pyogenes* ($n=9$)	*Streptococcus agalactiae* ($n=9$)
Age (months) [median (interquartile range)] (25–75%)	19 (11.2–35)	20 (7.7–48)	1 (0–9)	84 (18–126)	39 (20–72)	0 (0–1.5)
Previously healthy	66 (97.1)	42 (100)	28 (84.8)	20 (80)	9 (100)	7 (77.8)
Duration of fever < 12 h	21 (30.9)	17 (40.5)	20 (60.6)	7 (28)	3 (33.3)	9 (100)
Fever > 39°C	53 (77.9)	28 (66.7)	12 (36.4)	13 (52)	7 (77.8)	2 (22.2)
Associated symptoms						
None	16 (23.5)	8 (19)	18 (54.5)	7 (28)	0	4 (44.4)
Respiratory	30 (44.1)	4 (9.5)	7 (21.2)	0	0	0
Rash	0	17 (40.5)	0	0	3 (33.3)	0
Neurological	13 (19.1)	13 (31)	1 (3)	1 (4)	1 (11.1)	1 (11.1)
Stable on arrival	42 (61.8)	24 (57.1)	31 (93.9)	24 (96)	7 (77.8)	6 (66.7)
Physical examination						
None	25 (36.8)	8 (19)	27 (81.8)	7 (28)	1 (11.1)	4 (44.4)
Abnormal PA	21 (30.9)	0	0	1 (4)	0	0
Rash	8 (11.8)	32 (76.2)	1 (3)	2 (8)	5 (55.6)	0
CNS alteration	14 (20.6)	2 (4.8)	3 (9.1)	0	0	4 (44.4)
Final diagnosis						
Occult bacteraemia	25 (36.8)	2 (4.8)	2 (6.1)	8 (32)	3 (33.3)	2 (22.2)
Sepsis	8 (11.8)	30 (71.4)	3 (9.1)	1 (4)	2 (22.2)	6 (66.7)
Pneumonia	24 (35.3)	0	0	1 (4)	1 (11.1)	0
Urinary infection	0	0	26 (78.8)	1 (4)	0	0
Meningitis	8 (11.8)	10 (23.8)	2 (6.1)	0	0	1 (11.1)
OAI	0	0	0	13 (52)	3 (33.3)	0
Others	3 (4.4)	0	0	1 (4)	0	0
Evolution						
Death	2 (2.9)	0	0	0	1 (11.1)	0
Sequelae	5 (7.4)	3 (7.1)	0	0	0	0

CNS, central nervous system; OAI, osteoarticular and/or soft tissue infection; PA, pulmonary auscultation.

[a]Occult bacteraemia and meningitis were more common in children aged younger than 2 years (21/25, 84%; and 6/8, 75%, respectively). Most pneumonia cases were found in children aged older than 2 years (16/24; 66%).

[b]The presence of rash varied depending on the final diagnosis for the patient (29 of 30 patients (96.7%) with a final diagnosis of sepsis showed rash compared with 2/10 (20%) with meningitis, $P < 0.0001$).

[c]One of these was methicillin resistant.

main cause of shock and meningitis. The pneumococcal IBIs showed a different pattern depending on the age of the child. Bacteraemia and meningitis were more common in those aged younger than two years and pneumonia among older children. *S. pneumoniae* was involved in more than half the cases of children who died or who suffered sequelae. As a result, preventive actions, especially vaccination, appear essential [9]. A high percentage of the pneumococci isolated corresponded to vaccine serotypes, as noted previously [10]. In addition, the global prevalence of *S. pneumoniae* decreased after the implementation of the PCV13. This decrease would probably have been greater with adequate pneumococcal vaccination coverage of the population [11].

N. meningitidis accounted for the second latest group of IBIs; it was the main cause of sepsis and was associated with greater severity than the other bacteria. In contrast to other studies, which show a higher prevalence of meningococcal infections in children younger than 2 years of age [12], a large number of patients with meningococcal IBI were older than 2 years of age and 25% were older than 4 years. In contrast to other series [13,14], a significant percentage of patients did not develop a rash, mainly in patients diagnosed with meningococcal meningitis, making it more difficult to choose the best option of empirical antibiotics related to the presence or absence of rash [15]. The lower rate of rash in our patients, and perhaps the better overall evolution compared with other studies [16], could at least partially be explained by the fact that our patients are brought to the ED very early.

As it has been reported [17], *Staphylococcus aureus* was associated with osteoarticular and/or soft tissue infections in older children with more prolonged symptoms. Only one of the *S. aureus* isolated in our series was methicillin resistant. Given the recent increase in the prevalence of infections because of methicillin-resistant *S. aureus*, its prevalence must be considered when deciding on the most appropriate antibiotic [18].

As expected [17], infections caused by *Escherichia coli* and *Streptococcus agalactiae* were more common in younger children with fever without a source brought very early to the ED. Most of these patients were previously healthy and did not have a very high temperature.

Not appearing well when evaluated in the ED, the presence of symptoms other than fever and being brought early to the ED were associated with greater severity. This finding highlights the importance of early administration of antibiotics in patients with a suspected IBI.

Table 5 Clinical characteristics of the patients with an invasive bacterial infection who died or developed sequelae

Age (months)	Sex	Previously healthy	Previous visit	Time to progression (h)	Symptoms other than fever	Maximum temperatura (ºC)	Good general condition	Findings in physical examination	Bacteria	Diagnosis	Evolution
3	Male	Yes	Yes	72	Neurological	40.3	No	CNS	*S. pneumoniae*	Sepsis	Death
15	Female	Yes	No	8	Gastrointestinal	40	No	Signs of shock and rash	*S. pyogenes*	Sepsis	Death
114	Male	No	No	< 1 h	Headache	40.3	Yes	None	*S. pneumoniae*	Sepsis	Death
156	Female	No	No	Afebrile	Gastrointestinal	37.5	No	None	*M. morgagni*	Sepsis	Death
4	Female	Yes	No	24	Neurological	39	No	Signs of shock	*S. pneumoniae*	Meningitis	Hydrocephalus, deafness, endocarditis, VP shunt
8	Female	Yes	No	24	Rash	38.2	No	CNS and rash	*N. meningitidis*	Sepsis	Terminal kidney failure, transplant
24	Male	Yes	No	120	Respiratory	39.5	No	CNS and auscultation	*S. pneumoniae*	Sepsis	Necrotizing pneumonia, bronchopleural fistula
24	Male	Yes	Yes	120	Respiratory and digestive	40.2	No	CNS	*S. pneumoniae*	Pneumonia	Necrotizing pneumonia, bronchopleural fistula
37	Male	Yes	No	240	Respiratory and digestive	40	Yes	CPA	*S. pneumoniae*	Endocarditis	Valve replacement, metal prosthesis
39	Male	Yes	Yes	144	Respiratory	39	No	CPA and CNS	*S. pneumoniae*	Sepsis	Necrotizing pneumonia, bronchopleural fistula
64	Female	Yes	No	20	Gastrointestinal	39.2	No	CNS	*N. meningitidis*	Meningitis	Deafness
73	Female	Yes	Yes	16	Rash	39	No	Signs of shock and rash	*N. meningitidis*	Sepsis	Tissue necrosis

CNS, central nervous system; CPA, cardiopulmonary auscultation; CR, cardio-respiratory; VP shunt, ventriculoperitoneal shunt.

A worrisome finding was the number of children with a previous ED visit before diagnosis. Although this percentage was lower than reported previously [19], the patients diagnosed at a second visit in our study had a higher mortality and sequelae rate, although the differences were not significant. It has been suggested that progression to sepsis or meningitis in well-appearing children is unpredictable and therefore a careful clinical evaluation should normally be sufficient and the most appropriate at the first visit of a child with fever [20]. However, in light of our findings, it is advisable to recommend close monitoring by the parents in the following hours after the ED evaluation of febrile children and subsequent assessment by a primary care physician.

Our series has some limitations. First, it is a single-centre study with the limitations inherent to such studies. Thus, the rate of IBI is low, but we have to consider that the access to the ED in our country is free (it is not necessary to be sent from primary care or prehospital emergency settings) and around 20% of children admitted to our ED are trauma patients. Despite this, we consider that the findings are likely to be similar in other hospitals in Europe with similar vaccine coverage. Second, given the low incidence of occult bacteraemia in infants aged 3–24 months with fever without a source, in 2014, we increased the temperature cut-off point for collecting a blood culture, thus resulting in a marked reduction in the number thereof. However, the decrease in pneumococcal IBIs was not exclusively because of the decrease in the number of patients with occult bacteraemia as a decrease in other pneumococcal IBIs was also found, thus suggesting that the effect of the PVC13 is in agreement with published findings. Similarly, the low prevalence of opportunistic microorganisms in our series is mainly because of the fact that oncological patients were mainly managed by the paediatric oncology unit. However, we did not analyse the patients with a suspected invasive bacterial infection with no bacteria identified in blood or CSF. This would have enabled us to identify factors associated with a greater probability of having or not having an IBI, but this was not the objective of this study. We did not include some children who did not grow any organisms, but would have been defined as having sepsis (i.e. some extremely unwell children presenting who may have received antibiotics before cultures were obtained). This may impact on the overall burden of disease. Finally, as this is a retrospective study, data collection could occasionally have been improved. However, the fact that it is based on a prospective registry, the availability of electronic clinical records of the pediatric ED and the public health system electronic database enabled exhaustive data collection. This prospective registry has facilitated to get over the limitations due to the sample size found for the study conducted during the first 2 years [2].

Table 6 Univariate and multivariate analyses to identify the risk factors for severity in children diagnosed with an invasive bacterial infection

	Univariate		Multivariate	
	P	OR (95% CI)	*P*	OR (95% CI)
Age (>24 months)	0.691	1.123 (0.633–1.994)		
Sex (female)	0.257	1.395 (0.785–2.481)		
Previous visit to the emergency department	0.162	1.736 (0.802–3.759)		
Duration of fever (< 24 h)	0.080	1.740 (0.937–3.233)	< 0.001	4.082 (1.859–8.964)
Symptoms other than fever	< 0.001	4.935 (2.114–11.523)	0.005	3.869 (1.507–9.938)
Physical examination (altered)	< 0.001	4.825 (2.398–9.705)		
Temperature recorded upon arrival at the emergency department (≥39)	0.025	2.199 (1.104–4.382)		
Maximum temperature at home (< 39)	0.552	1.206 (0.651–2.234)		
Well-appearing (no)	< 0.001	8.910 (4.543–17.478)	< 0.001	8.286 (3.737–18.370)
Patient previously healthy (no)	0.062	2.421 (0.957–6.125)		

CI, confidence interval; OR, odds ratio.

In conclusion, paediatric IBIs currently present more frequently in previously healthy young children, with a clinical and epidemiological pattern that is highly dependent on the age of the patient and the bacterium isolated. The evolution of children with an invasive infection was generally good, although those patients who consulted with a shorter time to progression, symptoms other than fever or who did not present a good general condition upon arrival at the ED were associated with more severe processes. *Pneumococcus* spp. was responsible for more than half of the cases that resulted in death or the appearance of sequelae in these children.

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Conflicts of interest

There are no conflicts of interest.

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despite the highly variable baseline microbiota of patients with a tracheostomy.[7]

The traditional reductionist approach of categorizing ARIs as either viral or bacterial may be too simplistic a clinical framework for ARIs in individuals with a tracheostomy, and possibly all people with ARIs.[7] On D1 of ARI, the majority of the current prospective cohort had a virus detected and a "bloom" of already present genera (ie, *Haemophilus* and *Moraxella*). The tracheal finding of *Haemophilus* and *Moraxella* blooming are consistent with findings from previous studies utilizing nasopharyngeal samples to examine acute respiratory illness outcomes.[9] And although viral–bacterial interactions during ARIs have been described,[10] the present results extend previous research by suggesting that these ARIs were not infections due to acquisition of a new bacterial pathogen as Koch's postulates suggest, but rather a bloom of colonizing genera in the context of a viral infection. Conceptualizing ARIs as "blooms" may be more complex to operationalize clinically than the current reductionist approach, but may eventually provide opportunities for novel, targeted treatment methods. Although beyond the scope of these data, ARIs may be best understood as an emergent phenomenon[7] that (1) is driven by a complex interplay among the infecting virus, microbiome and host response[9] and (2) results in a continuum of ARI severity anchored by pneumonia.

The next step is to better understand the pathobiology of ARI in this high-risk population with variable underlying microbiota to develop novel targets for ARI treatment and to provide guidance about when to use antimicrobials and which bacteria to treat. Until this time of improved ARI understanding and clinical guidance, many clinicians will continue to overuse and misuse antimicrobials for ARIs in children with a tracheostomy.

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PREVALENCE OF OCCULT BACTEREMIA IN INFANTS WITH VERY HIGH FEVER WITHOUT A SOURCE

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Abstract: We carried out a prospective registry-based cohort study at the emergency department of 363 previously healthy well-appearing infants 3–24 months of age with fever without a source ≥40.5°C based on local protocol. Four were diagnosed with occult bacteremia (1.1%; 95% confidence interval: 0–2.2). Recommendations for nontesting for occult bacteremia screening in these children may have to be reconsidered when fever ≥40.5°C. Larger studies are needed to confirm these results.

Key Words: occult bacteremia, very high fever, fever without source, infants

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After the introduction of the pneumococcal conjugate vaccines (PCVs), pneumococcal invasive infections in febrile infants, including occult bacteremia (OB), declined dramatically.[1–3] In a cost-effectiveness study, it was stated that when the rate of OB in febrile infants falls below 0.5% strategies that use empiric testing and treatment should be eliminated.[4] On the other hand, if bacteremia rate is over 1.5%, it is cost-effective to obtain blood tests.[4] Currently, in vaccinated populations, the rate of OB in febrile infants is less than 0.5%. Nevertheless, these studies included infants with temperature greater than 39°C, and it is known that the prevalence of bacteremia increases at higher temperatures.[5] To our knowledge, no study has addressed the rate of OB in well-appearing, highly febrile infants in the era of PCV. The objective of this study is to analyze the prevalence of OB in previously healthy well-appearing infants 3–24 months of age with fever without a source (FWS) equal or higher than 40.5°C in the era of PCV.

PATIENTS AND METHODS

We carried out a registry-based cohort study at the pediatric emergency department (ED) of a tertiary level teaching hospital attending 55,000 visits annually. We included all previously healthy well-appearing infants 3–24 months of age with FWS ≥40.5°C brought to the ED between 2013 and 2016.

Each month, all the febrile infants with a blood culture obtained were identified using the electronic databases of the Microbiology Service and the ED. After that, the main investigator selected for inclusion all infants 3–24 months of age with FWS ≥40.5°C with a blood culture obtained when evaluated in the ED.

To check that all infants 3–24 months of age with FWS ≥40.5°C were included, we also reviewed a randomized sample of the patients coming to the ED during the period of the study. In this way, we revised all the episodes of children admitted to the ED 1 week per month during the period of the study.

We collected the following data from the electronic clinical records of our ED: age, gender, personal history, PCV status, duration of fever, associated symptoms, temperature, previous consultation in the ED, appearance on arrival, physical examination, different blood tests (white blood cell count, absolute neutrophil

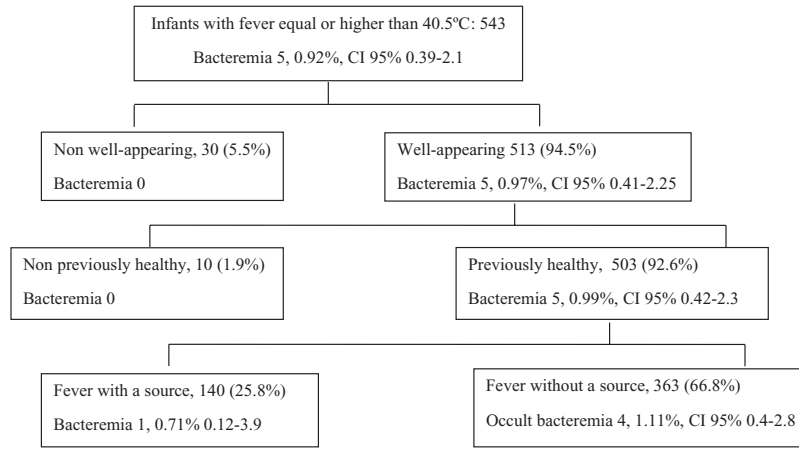

FIGURE 1. Patients' flow chart.

cell count, C-reactive protein and procalcitonin), microorganism isolated, final diagnosis and disposition of the patient.

In our ED, we recommend blood culture, white blood cell, absolute neutrophil cell, serum C-reactive protein, procalcitonin, urine dipstick and polymerase chain reaction for pneumococcus and meningococcus in all febrile infants 3–24 months old with FWS ≥40.5°C, regardless their vaccination status. Other tests (urine culture, chest radiograph, cerebrospinal fluid examination) were obtained at the discretion of the physician in charge.

Definitions

- Previously healthy patients: patients without any of the following risk factors: immunosuppression (oncologic illness, chronic renal failure, transplant patient, sickle cell disease), the presence of a mechanical device (indwelling catheter, ventricle-peritoneal shunt, auditory prostheses) and an invasive diagnostic or therapeutic procedure in the previous 10 days.
- Well-appearing patients: patients with a stable pediatric assessment triangle upon arrival at the ED. Pediatric assessment triangle is a rapid tool recommended by the American Academy of Pediatrics to assess the first general impression of any child. The appearance, the work of breathing and the circulation to the skin are evaluated using specific predefined physical, visual or auditory findings. If any of these 3 components is abnormal, the patient is considered unstable.
- FWS: axillary or rectal temperature higher than 38°C registered at home or in the ED, without associated respiratory symptoms, diarrhea process and findings on physical examination that allows identifying the source of the fever.
- OB: isolation of pathogenic bacterium in the blood of a well-appearing child with FWS.

PCV13 was included in the public immunization program in January 2013. Currently, PCV vaccination coverage in the Basque Country is around 95%.

We carried out the statistical analysis using the statistical program SPSS 23, Chicago, IL. The qualitative variables were described using absolute frequencies and percentages and the continuous variables were described using both the mean and standard deviation or median and interquartile range. The χ^2 test was used to study the association between qualitative variables.

The Clinical Research Ethics Committee of the hospital approved the study. To maintain patient confidentiality, the database did not include any data that would have allowed the identification of patients. As identities remained anonymous and no intervention was performed on patients, informed consent was not required.

RESULTS

During the study period, blood cultures were obtained on 543 infants 3–24 months of age with fever ≥40.5°C, including all the 363 previously healthy well-appearing infants with FWS ≥40.5°C (Fig. 1).

Mean age of the 363 previously healthy well-appearing infants with FWS ≥40.5°C was 13.9±4.9 months and 189 (52.1%) were female. PCV dosing was unknown in 23 (6.3%), and 51 (14%) had not received any dose. Fever duration was shorter or equal than 48 hours in 297 (81.8%). Most common final diagnoses were FWS 282 (77.7%); urinary tract infection 36 (9.9%); fever and rash 16 (4.4%); pneumonia 13 (3.6%) and bacteremia 4 (1.1%). All patients did well.

Four previously healthy well-appearing infants with FWS ≥40.5°C were diagnosed with OB (OB prevalence: 1.1%; 95% confidence interval [CI]: 0–2.2): 3 pneumococcal OB (one 16-month-old non-PCV vaccinated girl, and two 16-month and 19-month-old fully vaccinated girls; pneumococcal OB prevalence: 0.82%; 95% CI: 0%–1.8%) and a 12-month-old boy with a nontype b *Haemophilus influenza* bacteremia. All were managed as outpatients (3 of them after receiving 1 dose of IM ceftriaxone as a result of alterations of the blood biomarkers) and all did well.

Among those 289 infants who have received at least 1 dose of PCV, 2 were diagnosed with pneumococcal OB (0.69%; 95% CI: 0–1.6).

During the study period, blood cultures were also obtained in 140 previously healthy well-appearing infants with fever with a source ≥40.5°C (mainly respiratory symptoms). Blood culture was positive for *Streptococcus pneumoniae* in one 19-month-old boy fully vaccinated infant diagnosed with mastoiditis.

DISCUSSION

Although being lower than the reported in the pre-PCV studies,[4] the rate of OB in previously healthy well-appearing infants 3–24 months of age with FWS equal or higher than 40.5°C does not support the recommendation for not testing these infants to identify those at higher risk for OB. Even though the rate of bacteremia in fully PCV-immunized infants is 0.5% or greater.

Nowadays, most guidelines recommend not testing fully immunized (including PCV) febrile infants and do not give any specific recommendation for those with very high fever.[6] In fact, laboratory evaluation and empiric antibiotic therapy do not significantly

alter the likelihood of progression to focal bacterial infection and are no longer recommended in an otherwise healthy child with FWS who is completely immunized.[7] In addition, since the routine immunization of children with PCV7 or PCV13 vaccine, pathogens other than *S. pneumoniae* have being reported to be the cause of the majority of cases of unsuspected bacteremia.[8] In our study, 4 previously healthy well-appearing infants 3–24 months of age with FWS equal or higher than 40.5°C were diagnosed with OB, 3 of them caused by *Streptococcus pneumoniae*. Two were fully immunized. These results emphasize the importance to rule out serious bacterial infection in young high feverish children, including OB, and highlight the relevance of pneumococcal infection in this selected population in the era of the PCV.

Our study shows certain limitations. The main limitation is the sample size. The CIs of the obtained bacteremia rate do not allow giving a strong recommendation for this population. Nevertheless, the results obtained emphasize the importance to carry out a larger study, preferably multicenter, to establish if nontesting strategy is adequate when fever is over 40.5°C. On the other hand, this is a unicenter study. Nevertheless, results should be similar in populations with similar vaccination status. Finally, to include all the patients in a prospective way, collecting the data when the infants are in the ED would have been more adequate to include all patients. Nevertheless, with the random revision of the episodes registered in the ED, we think that only very few patients were missed, if any.

We conclude that, despite recommendations for nontesting for pneumococcal OB screening in well-appearing febrile infants, these recommendations may have to be reconsidered in infants with FWS ≥40.5°C, including those fully vaccinated. Larger and preferably multicenter studies are needed to confirm these results. Accordingly, a prospective multicenter study will begin on 2018 under the scope of the Research network of the Spanish Society of Pediatric Emergency Medicine (Red de Investigación de la Sociedad Española de Urgencias de Pediatría-Spanish Pediatric Emergency Research Group RISEUP-SPERG).

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I.K. conceptualized and designed the study, supervised data collection, analyzed the data, wrote the initial draft of the manuscript and approved the final manuscript as submitted. E.R. collaborated in the design of the study, collected data, critically revised the manuscript and approved the final manuscript as submitted. A.Z. collected data, critically revised the manuscript and approved the final manuscript as submitted. J.B. collaborated in the design of the study, critically revised the final manuscript and approved the final manuscript as submitted. S.M. conceptualized and designed the study, analyzed the data, revised multiple versions of the initial manuscript and approved the final manuscript as submitted.

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CARDIAC AND PULMONARY CYSTIC ECHINOCOCCOSIS WITH MASSIVE OBSTRUCTION OF THE PULMONARY VESSEL SYSTEM IN A 16-YEAR-OLD GIRL

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Abstract: We describe herein the management of a 16-year-old girl with cystic echinococcosis of the right ventricle and massive obstruction of the pulmonary vessel system by parasitic metastatic dissemination. After resection of the cardiac cyst, pulmonary thromboendarterectomy was performed to remove parts of the obstructive parasitic material. The treatment reduced the elevated pulmonary arterial pressure, improving the patient's overall condition.

Key Words: cystic echinococcosis, thromboendarteriectomy, pulmonary intravascular cyst, cardiac cyst, albendazole, praziquantel

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Cystic echinococcosis (CE), caused by *Echinococcus granulosus*, is a common parasitic disease with high incidence rates in rural areas in Southern Europe, Middle East, Asia and Africa.[1,2] In rare cases, it primarily affects the heart. Ruptures of the cyst membranes can lead to cardiac tamponade, anaphylactic shock or embolization and obstruction of pulmonary vessels, resulting in severe cardiopulmonary symptoms.[3,4] Here, we present a complex case with cardiac and pulmonary involvement and massive obstruction of the pulmonary arteries.

CASE REPORT

A 16-year-old previously healthy female was admitted to our hospital with a 2-month history of increasing dyspnea and coughing. She grew up in a CE endemic area in Romania and moved to Austria 2 years ago. She lived together with her family and was working as a waitress.

Physical examination showed normal weight and height, normal heart rate, no cardiac murmur, normal blood pressure, normal breathing, no dyspnea at rest and no edema. Oxygen saturation was 93%–96% at normal respiratory rate.

Chest radiograph showed multiple intrapulmonary nodules in both lungs and widening of the upper mediastinum. Echocardiography revealed a cystic lesion in the apex of the right ventricle (Fig. 1A). Thoracic computed tomographic scan displayed a cystic

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COVID-19 infection in children shows unique features. All published series agree on its usual mildness, with a high proportion of asymptomatic patients and very low mortality. However, an association between SARS-CoV-2 infection and the appearance of a very serious clinical picture, called pediatric multisystem inflammatory syndrome, has been described.[2,7] Pathophysiology of MIS-C is still unclear. In a recent case series, children with MIS-C had significantly higher SARS-CoV-2 binding and neutralizing antibodies than children with COVID-19 or Kawasaki Disease. MIS-C might be different from other syndromes with similar clinical appearances, with features including an age at onset greater than 7 years, diffuse cardiovascular involvement and elevated quantitative SARS-CoV-2 binding and neutralizing antibodies.[8]

Gastrointestinal symptoms are increasingly recognized to be associated with the presentation of MIS-C. In 2 recently reported series of 35 and 44 pediatric patients with MIS-C, more than 80% showed some type of digestive involvement.[9,10] In our study, 11 patients with MIS-C were included, all of them showing GI symptoms.

Our study has several strengths. It is a multicenter study, involving 15 hospitals in Spain, one of the most impacted countries during the pandemic in Europe. As a consequence, our sample is probably the largest published in pediatric hospitalized patients with COVID-19.

As a limitation of the study, we want to acknowledge the fact that although the development of the project started early in the course of the pandemic in Spain, the majority of the data were retrospectively retrieved.

In conclusion, gastrointestinal symptoms are frequent in COVID-19 pediatric patients admitted to hospital. These symptoms are also predictive of severity, regardless to other confounding factors.

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OCCULT BACTEREMIA IN YOUNG CHILDREN WITH VERY HIGH FEVER WITHOUT A SOURCE: A MULTICENTER STUDY

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Abstract: We carried out a prospective multicenter study including 203 previously healthy well-appearing children who were 3–24 months old with fever without a source ≥40.5°C. Thirty-one (15.3%, 95% confidence interval 11.0–20.9) were diagnosed with serious bacterial infection, including 6 with bacteremia (3%, 95% confidence interval 1.4–6.3). Testing for occult bacteremia in children 3–24 months old with fever without a source should be considered when fever at ≥40.5°C.

Key Words: prevalence, occult bacteremia, very high fever, pneumococcal

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The rate of occult bacteremia in young febrile children has declined dramatically after the introduction of the pneumococcal conjugate vaccines (PCV).[1–3] In this way, strategies that use empiric testing and treatment in young febrile children with temperature higher than 39°C are no longer recommended.[4,5] Nevertheless, previous to the PCV era, the prevalence of bacteremia increased at higher temperatures.[6] Currently, in a unicenter study, the rate of occult bacteremia in previously healthy well-appearing young children who were 3–24 months old with fever without a source (FWS) ≥40.5°C was 1.1% [95% confidence interval (CI) 0–2.2],[7] being PCV vaccination coverage in Spain around 98%.[8] Though, before re-considering the recommendation for testing these young children for occult bacteremia, a multicenter was warranted.

The main objective was to analyze the prevalence of occult bacteremia in previously healthy well-appearing young children 3–24 months of age with FWS equal or higher than 40.5°C in the era of PCV.

PATIENTS AND METHODS

We carried out a multicenter, prospective, observational study at 6 Spanish pediatric emergency departments (ED) on behalf of the Infectious Diseases Working Group of the Spanish Society

TABLE 1. Characteristics of Patients Diagnosed With Bacteremia

Age (Months)	Sex	Duration of Fever (Hours)	PCV Status	Meningococcal Vaccine	Urine Dipstick	WBC	ANC	CRP	PCT	Antibiotic Received	Admission to Ward	Bacteria	Disposition
13	Female	18	3 doses	1 dose	Normal	18,400	9300	75.9	0.23	Yes. Ceftriaxone	No, outpatient	*Streptococcus pneumoniae* (serotype unknown)	Discharge, no sequelae
14	Male	48	3 doses	2 doses	Normal	16,800	12,000	259.1	9.52	Yes. Ceftriaxone	Yes	*Streptococcus pyogenes*	Discharge, no sequelae
11	Female	24	3 doses	1 dose	Normal	24,600	13,100	31.8	3.10	Yes. Ceftriaxone	No, outpatient	*Streptococcus pneumoniae* (serotype 24F)	Discharge, no sequelae
13	Female	18	2 doses	2 doses	Non performed	9400	6100	320	32	Yes. Ceftriaxone	Yes	*Neisseria meningitidis* (serogroup unknown)	Discharge, no sequelae
16	Male	20	3 doses	No	Normal	25,700	22,200	66	5.96	Yes. Ceftriaxone	Yes	*Streptococcus pneumoniae* (serotype 38)	Discharge, no sequelae
23	Female	48	3 doses	No	Normal	18,500	11,100	77.5	0.19	Yes. Ceftriaxone	No, outpatient	*Moraxella spp.*	Discharge, no sequelae

of Pediatric Emergencies, endorsed by the Research network of the Spanish Society of Pediatric Emergency Medicine.

Patients were prospectively enrolled starting from January 1, 2018 to December 31, 2019. We included all previously healthy well-appearing 3–24-month-old children with FWS ≥40.5°C brought to the ED.

We collected the following data from the patient ED episode: age, sex, personal history, vaccination status, duration of fever, associated symptoms, temperature, previous consultation in the ED, appearance on arrival, physical examination, supplementary tests, isolated microorganism, final diagnosis and disposition of the patient. We monitored the progress of the patients by reviewing the medical records of those who were admitted to ward, and by primary care medical reports and conducting telephone interviews for those who were managed as outpatients. Interviews were performed within a month after the visit to the ED.

Obtaining a blood culture in the included children was mandatory and we also recommended to obtain the following tests: white blood cell count (WBC), absolute neutrophil count (ANC), serum C-reactive protein (CRP) and procalcitonin (PCT). These tests were considered to be altered if WBC was lower than 5000/µL or higher than 15,000/µL, ANC >10,000/µL, CRP >20 mg/L and PCT >0.5 ng/mL. The polymerase chain reaction for pneumococcus and meningococcus was obtained in those EDs in which this test was available. Urine dipstick was performed in all 3–24-month-old female and 3–12-month-old male children. Other tests (urine culture, chest radiograph, cerebrospinal fluid examination) were obtained at the discretion of the physician in charge.

All included children had specific electronic questionnaires completed via Google Drive by the physicians in charge of their care. Questionnaires were initially distributed to all participating EDs seeking to ensure the clarity of the methods and to enhance the quality of the data collected. The questionnaires were then completed by the physician after ED discharge for patients discharged home, and after hospital discharge for patients admitted to the hospital, to obtain complete information on patient characteristics and ED and outcomes. The completed questionnaires were then sent to the principle investigator (I.G.).

Definitions were explained in the previous manuscript.[7] FWS was considered in febrile children without associated respiratory symptoms (including rhinorrhea or nasal congestion), diarrhea process and findings on physical examination (including acute otitis media) that allows identifying the source of the fever. We considered to be previously healthy patients those without any of the following risk factors: immunosuppression (oncologic illness, chronic renal failure, transplant patient, sickle cell disease), the presence of a mechanical device (indwelling catheter, ventricle-peritoneal shunt, auditory prostheses) and an invasive diagnostic or therapeutic procedure in the previous 10 days. For this study, we considered serious bacterial infection those children finally diagnosed with bacteremia, urinary tract infection, bacterial meningitis or pneumonia.

We carried out the statistical analysis using the statistical program SPSS 23, Chicago, IL. We described the categorical variables using absolute frequencies and percentages and the continuous variables using both the mean and standard deviation or median and interquartile range. We used the χ^2 test to study the association between categorical variables.

The Clinical Research Ethics Committee of the Basque Country approved the study (internal code PI2017169). Approval for study and data sharing with the coordinating institution and with the centralized data center was granted by the institutional review board at each participating institution. To maintain patient confidentiality, the forms did not include any data that would have allowed the identification of any patient.

RESULTS

During the study period, we registered 344,500 episodes in the 6 pediatric EDs. Of them, 203 corresponded to children 3–24 months of age with FWS equal or higher than 40.5°C. Mean age was 14 ± 4.6 months old and 110 (54.2%) were male. Two hundred (98.5%) had received at least 1 PCV dose and 103 (50.7%) had a duration of the fever less than 24 hours. Thirty-one (15.3%, 95% CI 11.0–20.9) were diagnosed with serious bacterial infection: urinary tract infection 14 (6.9%), pneumonia 11 (5.4%) and bacteremia 6 (3%). All blood tests (CRP, PCT, WBC and ANC) were obtained in 192 children. Thirty (15.6%) did not show any alteration of the tests, including 1 child diagnosed with pneumonia and 1 with UTI. Lumbar puncture was performed in 3 patients (negative cultures); urine dipstick in 169 (83.3%), urine culture in 75 (36.9%) and chest radiography in 97 (47.7%).

The characteristics of young children diagnosed with bacteremia are shown in Table 1. All children with bacteremia had, at least, 1 blood test altered (sensitivity 100%, 95% CI 51.7–100; specificity: 16.1%, 95% CI 11.3–22.4; PPV: 3.7%, 95% CI 1.5–8.2). All febrile children with bacteremia did well. Of the 6 children diagnosed with occult bacteremia, 3 corresponded to children with pneumococcal occult bacteremia [prevalence 1.48%; (95% CI 0.5–4.3)].

DISCUSSION

The rate of occult bacteremia in previously healthy well-appearing children 3–24 months of age with FWS equal or higher than 40.5°C supports the recommendation for testing these children for occult bacteremia, regardless the PCV vaccination status. The results of our study confirm those obtained in the previous unicenter study.[7] In addition, all the children diagnosed with occult bacteremia were fully PCV vaccinated, including those with pneumococcal occult bacteremia. Pneumococcal occult bacteremia may occur in PCV fully vaccinated children.[9] In fact, PCV13 serotypes continue to account for nearly a quarter of invasive pneumococcal infection in US children 4–7 years after PCV13 was introduced, mainly otherwise healthy children despite receiving ≥2 PCV13 doses.[9]

Recommendation for no additional testing beyond evaluation of the urine should be reconsidered in children 3–24 months with FWS ≥40.5°C. The role of blood tests to guide initial clinical decision-making in these patients, like administering antibiotics, should be determined. In the pre-PCV era, one option for the management for young febrile children higher than 39°C was to administer antibiotics to those young children with altered WBC and/or ANC[10], although positive predictive value of test results was poor. Currently, new tests are often used to evaluate febrile children at risk for invasive bacterial infection at the ED. It would be interesting to know if PCT and CRP are more adequate to identify young children with high fever at high risk for bacteremia. In our study, all the children with occult bacteremia showed alterations of the biomarkers, but global performance of the tests was also poor.

Our study shows certain limitations. The main limitation of our study is the sample size. In the previous unicenter study,[7] we commented that larger and multicenter studies were necessary to confirm the results obtained. In this way, when designing this prospective multicenter study our intention was to include around 1000 patients. After including 200 patients with a rate of bacteremia around 3%, we thought that it was not adequate to continue recruiting patients and not publishing our results.

We conclude that previously healthy and well-appearing 3–24-month-old children with FWS equal or higher than 40.5°C should be tested for occult bacteremia regardless of their PCV vaccination status.

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PLASMAPHERESIS FOR RESCUE IN SEVERE ENCEPHALOPATHY AND MULTIORGAN FAILURE FROM FULMINANT INFLUENZA (H3N2) INFECTION

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Abstract: We are presenting a case of 4-years-old previously healthy male with coma, severe acute hepatitis and multiorgan failure in presence of Influenza infection. Literature review highlighted an immune-mediated pathophysiology for such presentations so the child underwent a trial of plasmapheresis which resulted in a rapid clinical improvement and child was discharge in his baseline neurologic status by day 14.

Key Words: immune mediated encephalitis, plasmapheresis, influenza, multiorgan dysfunction

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REGULAR ARTICLE

ACTA PÆDIATRICA NURTURING THE CHILD WILEY

Paediatric *Escherichia coli* bacteraemia presentations and high-risk factors in the emergency department

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Abstract

Aim: *Escherichia coli* (*E coli*) is a known cause of paediatric bacteraemia. The main objective was to characterise the emergency department (ED) presentations of paediatric *E coli* bacteraemia and secondarily to identify those related to greater severity.

Methods: This was a sub-study of a multicentre cross-sectional prospective registry including all with *E coli* bacteraemia episodes between 2011 and 2016. We used multiple correspondence and cluster analysis to identify different patterns.

Results: We included 291 patients and 43 met criteria for severe disease (14.3%, 95% confidence interval 11.2-19.3). We identified four types of paediatric *E coli* bacteraemia presentations. Two (178 patients, 61.2%) were related to well-appearing previously healthy infants with associated urinary tract infection (UTI). Well-appearing children older than 12 months old with underlying disease (n = 60, 20.6%) and non-well-appearing children of different ages (n = 53, 18.2%) corresponded to the other two types; these had associated UTI infrequently and higher severity rate (15% and 50.9%, respectively, higher when compared with the two previous types, $P < .01$), including the two patients who died.

Conclusion: There were four different types of ED paediatric *E coli* bacteraemia presentations with different severity. Febrile young children with associated UTI showed the best outcome.

KEYWORDS

bacteraemia, *Escherichia coli*, outcome, risk factor, urinary tract infection

1 | BACKGROUND

Fever is a very common reason for consultation among children attending the emergency department (ED). In most cases, the cause is a self-limiting viral infection. Despite advances in vaccinations and antibiotics, invasive bacterial infections remain significant causes of death of children in developed countries. General infant immunization programmes against the most common pathogens (*Haemophilus influenzae type b*, *Streptococcus pneumoniae* and *Neisseria meningitides*) have led to a significant decrease of childhood invasive

Abbreviations: *E. coli*, Escherichia coli; ED, emergency department; ICU, intensive care unit; UTI, urinary tract infection.

bacterial infections[1,2] and changes in the distribution of most frequently isolated pathogens.

Escherichia coli is a known cause of bacteraemia in febrile infants under 12 months of age[3] and has been widely reported mainly in febrile infants <3 months of age, many of them associated with a urinary tract infection (UTI).[4,5] In a previous study under the scope of the Spanish Society of Emergency Medicine, *E coli* accounted for 20% of the bacteraemia episodes registered in previously healthy children in Spanish EDs.[6] To our knowledge, no large series have analysed the clinical presentation and outcome of children with *E coli* bacteraemia. Our study may help to better identify these children in the ED, especially those at higher risk for severe disease.

The main objective was to characterise the ED presentations of paediatric *E coli* bacteraemia. The secondary objective was to identify presentations related to higher severity.

Our hypothesis was that there are different profiles of paediatric *E coli* bacteraemia presentations with different risk for severe illness.

Key notes

- We characterised the emergency department presentations of paediatric *E coli* bacteraemia and identified those related to greater severity in 291 patients <18 years of age.
- We identified four types of presentations related to previous illnesses, age, sex, appearance upon the arrival and association with urinary tract infection.
- Association with urinary tract infection in febrile well-appearing previously healthy young children showed the best outcome.

2 | PATIENTS AND METHODS

We performed a secondary analysis of a large, multicentre, cross-sectional prospective registry of childhood bacteraemia presentations to 23 Spanish EDs.

In 2010, the Spanish Society of Paediatric Emergency Medicine proposed the establishment of a prospective multicentre registry of positive blood culture obtained at Spanish paediatric EDs. Patients between 0 months and 20 years were prospectively enrolled between 2011 and 2016. During 2011, 15 paediatric EDs participated in the recruitment, 22 during 2012, 21 during 2013, 19 during 2014, 17 during 2015 and 13 during 2016.

Blood culture technique was explained in the study published in 2014.[6]

For the purpose of this study, we included those children with *E coli* isolated in the blood culture.

We used the Paediatric Assessment Triangle (PAT) to assess the first general impression of the child. The PAT is a rapid tool recommended by the American Academy of Pediatrics to assess the first general impression of any child. The appearance, the work of breathing and the circulation to the skin are evaluated using specific predefined physical, visual or auditory findings. If any of these three components are abnormal, the patient is considered as non-well appearing.[7]

Certain factors were considered as increasing the risk of having a bacteraemia. These factors included immunosuppression such as oncological illness, chronic renal failure, transplant patient and sickle cell disease; the presence of a mechanical device, such as an indwelling catheter or a ventriculo-peritoneal shunt; an invasive diagnostic or therapeutic procedure in the previous 10 days; a serious kidney or urinary tract malformations such as double renal system, severe bilateral vesicoureteral reflux and presence of ureterostomy or vesicostomy; and patients with multiorgan syndromes or systemic illness. For the purpose of this study, patients without any of these risk factors were considered previously healthy.

We defined occult bacteraemia as isolation of *E coli* in the blood in the absence of an identifiable focus of infection. A new positive blood culture after adequate antibiotic treatment (sensitive antibiogram and adequate dose and duration of the antibiotic) was considered as a new episode of bacteraemia.

For the purpose of this study, we adapted the sepsis criteria published by Goldstein et al[8] A patient with a positive blood culture was diagnosed with sepsis if presenting with any of the following signs: tachycardia >180 bpm not due to external or painful stimuli or long-term medication; bradycardia <100 bpm not due to external vagal stimulus, β-blocker drugs or congenital heart disease (only applicable in infants younger than 1 year old); tachypnoea >50 rpm; and signs of organ dysfunction as listed in the aforementioned publication.[8]

Septic shock was considered in those patients with persisting hypotension requiring vasopressors despite adequate resuscitation.

Higher severity was considered when children met one or more of the following criteria: death, sequelae, admission to the intensive care unit (ICU), sepsis, meningitis and/or acute complications including renal or hepatic failure, stroke, acute respiratory distress syndrome or catheter replacement.

We created two forms to be completed online using Google Drive application (Google LLC). Questionnaires were initially distributed to all participating EDs seeking to ensure the clarity of the methods and to enhance the quality of the data collected and were fulfilled by the site investigators. The first questionnaire was a patient registration form for each positive blood culture collected, with epidemiological and clinical data, the results of tests performed, final diagnosis and outcome. A second form was used to provide the following additional, monthly data: total number of patients attended, of blood cultures taken and of positive blood cultures obtained.

Only the research coordinator had access to the two resulting online databases, being responsible for downloading regular backups of both databases and reviewing them for possible errors in data

entry. The participating researcher in each centre was responsible for reviewing the episodes with potential errors.

To identify types of *E coli* bacteraemia presentations, we used multiple correspondence analysis and cluster analysis. In order to perform multiple correspondence analyses,[9] we used the following categorical variables: sex, age, PAT, previously healthy, fever, other symptoms and physical examination. Age was categorised into <3 months, 3-12 months and >12 months; PAT into normal, altered appearance, altered circulation to the skin and altered work of breathing. We then performed the cluster analysis, which organises information from apparently heterogeneous episodes into relatively homogenous groups. We used the factors obtained in the multiple correspondence analyses as variables to perform the cluster analysis and to obtain the appropriate grouping of *E coli* bacteraemia presentations.[10] To create clusters, we used the squared euclidean distance and Ward method.[11] This method combined correspondence analysis and cluster analysis to categorise *E coli* bacteraemia cases into groups. These groups were suggested by the data and not defined a priori. The groups were made in a way such that cases in a given group of *E coli* bacteraemia were similar to each other and those in different groups were dissimilar.

Finally, chi-square test was used to study the association between severity and different types of *E coli* bacteraemia presentations. Outcome measure was the presence of, at least one of the severity criteria described previously.

We performed all statistical analyses using SPSS vs. 23.0 statistical software and R project, version 3.6.2 'Dark and Stormy Night' (IBM).

This study was approved by the Ethical Committee of the Basque Country (registration number PI2011040). Approval for the study and for data sharing with the coordinating institution and with the centralised data centre was granted by the institutional review board at each participating institution. To maintain patient confidentiality, the forms did not include any data that would have allowed the identification of any patient.

3 | RESULTS

During the time of the study, we registered a total of 3 936 827 ED episodes, of which a positive blood culture was isolated in 1696 (0.04%, CI 95% 0.04-0.05). In 291 (17.6%, 95% CI 15.4-19.0), blood culture was positive for *E coli*. Table 1 reports descriptive statistics for the main epidemiological variables, management and outcome of the children with *E coli* bacteraemia.

Final diagnosis were UTI with associated bacteraemia 206 (70.8%); occult bacteraemia 27 (9.3%); sepsis/shock 32 (11%, three of them with associated meningitis); meningitis 5 (1.7%); catheter-associated bloodstream infection 6 (2.1%); and others 15 (5.1%). Of the 291 patients, 43 (14.8%, 95% CI 11.2-19.3) were considered to have severe illness (Table 2). Two patients died.

The multiple correspondence analyses rand cluster analysis identified four main types of paediatric *E coli* bacteraemia presentations (Table 3). Two types of *E coli* bacteraemia presentations (groups A and B) were mainly related to well-appearing previously healthy infants <12 months old with associated UTI (85.0% and 98.5%,

TABLE 1 Epidemiological and clinical characteristics, complementary tests, management and disposition of the patients with *E coli* bacteraemia

Age (in months)[a]	3 (1-11)
Sex (female)	131 (45%)
Non- previously healthy patients	67 (23%)
Immunosuppression	27 (9.3%)
Patients with multiorgan syndromes or systemic illness	16 (5.4%)
Serious kidney or urinary malformations[b]	13 (4.5%)
Presence of a mechanical device	7 (2.4%)
Invasive diagnostic or therapeutic procedure in the previous 10 d	4 (1.4%)
Duration of the fever (in hours)[a]	12 (3-24)
Temperature upon arrival to the emergency department (°C)[c]	37.9 ± 1.0
Well appearing upon arrival to the emergency department	244 (83.8%)
No findings in the physical examination	226 (77.7%)
Urine culture performed	263 (90.4%)
Lumbar puncture performed	71 (24.4%)
Chest X-ray performed	33 (11.3%)
Administered antibiotic	284 (97.6%)
Admission to ward/Intensive care unit	255 (87.6%)

Note: Data are expressed as n and percentage.

[a]Age and evolution time are expressed as median and interquartile range.

[b]Serious kidney or urinary malformations: double renal system, severe bilateral vesicoureteral reflux and presence of ureterostomy or vesicostomy.

[c]Temperature is expressed as mean ± standard deviation.

respectively, compared with 50% and 30.2% of groups C and D). The main differences between groups A and B were the age and the sex, but, overall, they did well. Group A included mostly males younger than 3 months of age (81.4%) and group B mainly females (87.7%) 3-12 months old. Rate of severity was 5.3% and 3.1%, respectively.

Well-appearing children older than 12 months with underlying diseases accounted for the majority of the third group of patients (group C). The last group (group D) included non-well-appearing children of different ages, one-third of them non-previously healthy. Associated UTI was significantly lower in these two groups (group C = 50.0%, group D = 30.2%), and the rate of severity was 15% and 50.9%, respectively (significantly higher than in groups A and B, $P < .01$). The two patients who died were included in group D.

Eight children were diagnosed with bacterial meningitis (three of them with associated sepsis). All of them were younger than 5 months. The rate of associated meningitis in febrile infants with *E coli* bacteraemia is shown in Table 4.

TABLE 2 Number of patients with each severity criteria

Severity criteria	N (%)
Sepsis	32 (11.0)
Admission to the intensive care unit[a]	22 (7.6)
Acute complications	8 (2.7)
Meningitis	8 (2.7)
Sequelae	7 (2.4)
Death	2 (0.7)

Note: Data are expressed as n and percentage. Twenty patients (6.9%) presented a single severity criteria.

Sixteen patients (5.5%) presented two severity criteria.

Seven patients (2.4%) presented three or more severity criteria.

[a]There is no patient with this severity criteria exclusively.

4 | DISCUSSION

Our data suggest four different types of paediatric *E coli* bacteraemia presentations to the ED with different degree of severity. Association with UTI in children less than a year was most common, whereas older age was associated with greater severity, mainly when the child was unwell upon presentation to the ED.

Many children did not have high fever and abnormal findings in the physical examination were uncommon. In addition, the majority of these children appeared well when evaluated in the ED. This underlines the importance of having a high index of suspicion in selected patients.

E coli is the most common pathogen involved in invasive bacterial infections in young febrile infants.[3,5] Many of these are associated with UTI, which is the most common serious bacterial infection in young febrile infants.[12] Young febrile infants with UTI are more prone to have associated bacteraemia.[12] Around 5% of febrile infants <3 months of age with UTI have an associated bacteraemia, with the highest risk in infants <28 days.[13] Traditionally, it has been recommended to hospitalise young febrile infants with suspected UTI due to the concern of acute adverse events and for missing concomitant bacteraemia. During the last years, efforts have been made to identify young febrile infants <3 months with suspected UTI at low risk for bacteraemia and suitable for outpatient management.[14,15] Several studies have assessed the course of febrile infants with UTIs and suggest that otherwise well-appearing infants with or without concomitant bacteraemia have benign clinical outcomes when treated with appropriate antibiotics.[16-18] Our study may support a less conservative management. In fact, in our study, only around 5% of febrile infants with *E coli* bacteraemia had a severe disease, including those <3 months of age. Nevertheless, all except one of the children with bacterial meningitis were younger than two months of age. Nearly 10% of

TABLE 3 Main types of paediatric *E coli* bacteraemia presentations

Variable		A (n = 113, 38.8%)	B (n = 65, 22.3%)	C (n = 60, 20.6%)	D (n = 53, 18.2%)	*P* value
Sex	Female	21 (18.6%)	57 (87.7%)	36 (60%)	17 (32.1%)	<.001
Age	<3 mo	95 (84.1%)	10 (15.4%)	3 (5%)	24 (45.3%)	<.001
	3-12 mo	18 (15.9%)	55 (84.6%)	6 (10%)	15 (28.3%)	
	>12 mo	0	0	51 (85%)	14 (26.4%)	
Previously healthy	No	3 (2.7%)	0	47 (78.3%)	17 (32.1%)	<.001
Fever[a]	Yes	88 (77.9%)	65 (100%)	58 (96.7%)	41 (77.4%)	<.001
Other symptoms	Yes	24 (21.2%)	40 (61.5%)	30 (50%)	45 (84.9%)	<.001
Paediatric assessment Triangle	Altered appearance	1 (0.9%)	1 (1.5%)	2 (3.3%)	35 (66%)	<.001
	Altered circulation	1 (0.9%)	0	1 (1.7%)	18 (34%)	
	Altered breathing	0	0	0	6 (11.3%)	
Physical examination	Altered	7 (6.2%)	5 (7.7%)	8 (13.3%)	45 (84.9%)	<.001
Associated UTI	Yes	96 (85%)	64 (98.5%)	30 (50%)	16 (30.2%)	<.001

Note: Data are expressed as n and %. The *P* values demonstrate the differences between groups among the analysed variables.

[a]Temperature higher than 38°C at home and/or at the emergency department.

TABLE 4 Rate of associated meningitis in febrile infants with *E coli* bacteraemia related to the age

Group of age	Rate of bacterial meningitis
<1 mo old	6/64, 9.4%, 95% CI 4.4-19
1 mo old	1/38, 2.6%, 95% CI 0.5-13.5
2 mo old	0/30, 0, 95% CI 0-11.3
3-24 mo old	1/107, 0.9%, 95% CI 0.2-5.1

Note: Data are expressed as n, percentage and confidence interval.
Abbreviation: CI, confidence interval.

febrile infants younger than 1 month old with *E coli* bacteraemia had associated bacterial meningitis. Higher risk of meningitis associated UTI has been previously published in febrile neonates.[16] Our study supports the decision of making a cerebrospinal fluid examination in febrile neonates with confirmed or suspected *E coli* bacteraemia.[15]

Although the diagnosis of bacterial meningitis is very rare in older children with *E coli* bacteraemia, severe illness is more common in these patients. In our series, around 50% of non-well-appearing children with *E coli* bacteraemia had a severe disease, including two children who finally died. This emphasises the importance to consider UTI in those non-well-appearing febrile children and, if possible, to collect a urine culture before initiating the antibiotics. This also confirms that PAT is a reliable tool to identify children with severe illness upon the arrival to the ED.[7]

Finally, the group of older febrile children with underlying diseases had a 15% rate of severe disease. This underscores the importance of a more cautious management of children with underlying diseases because of the high risk of invasive infections when these children present to the ED.[19,20]

Our study shows certain limitations. Our registry was not designed to characterise the ED presentations of paediatric *E coli* bacteraemia. Nevertheless, we think that collected data allow us to define the different types of these presentations and to relate them with severity. This study was conducted to identify risk factors in children with *E coli* bacteraemia and not UTI. In addition, *E coli* is not the single pathogen responsible for UTI especially in children with underlying diseases. Thus, our results cannot be extrapolated to febrile UTI. Finally, we think that defining the indications for cerebrospinal fluid examination would require a specific larger study. Nevertheless, our data support to strongly consider cerebrospinal fluid examination in infants <2 months old with *E coli* bacteraemia.

5 | CONCLUSION

We conclude that there are four different types of paediatric *E coli* bacteraemia presentations to the ED with different rate of severity. UTI-associated bacteraemia in infants <12 months were most common but those involving older children account for large amount of patients and are related to higher risk, mainly when the child is unwell upon the arrival to the ED. Associated bacterial meningitis is rare in children older than two months of age.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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Markers for invasive bacterial infections in previously healthy children

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1. Introduction

Most previously healthy febrile children have self-limited viral infections. However, sometimes, fever is due to an invasive bacterial infection (IBI). Prompt identification of these children is essential to initiate an early and appropriate treatment. Nevertheless, this identification may be difficult. In a recent study, 22% of children with bacterial meningitis or sepsis had repeated emergency department (ED) visits before admission [1]. Currently, these children are often brought very early to the ED, and signs and symptoms of children with an IBI can be difficult to distinguish from self-limited febrile illnesses [2]. Furthermore, most of these patients are younger than 2–3 years-old, being the clinical expression of different infections more unspecific.

Therefore, physicians may not be confident enough in the physical exam and seek for blood tests like white blood cell count (WBC) or the absolute neutrophil count (ANC) to guide initial clinical decision-making in certain febrile children. In the last decades, C-reactive protein (CRP) and procalcitonin (PCT) have emerged as valuable risk-stratification tests to identify high-risk infants [3]. To analyze the response of blood biomarkers commonly used in the ED in children with microbiologically confirmed IBIs seems important.

Our hypothesis is that the response of the blood tests to IBI varies related to the causative pathogens and the final diagnosis.

The objective of the study is to analyze the markers' profile in previously healthy children when evaluated in the ED and finally diagnosed with an IBI: WBC, ANC, CRP and PCT.

2. Patients and method

This was a retrospective, descriptive study based on a registry of a cohort of children under 14-years-old microbiologically diagnosed with an IBI in a pediatric ED of a tertiary teaching hospital in Spain between January 2008 and May 2020.

We identified patients with IBI from the hospital's electronic records as we have previously described [4]. We obtained the information of the patients from the electronic clinical records of the pediatric ED and Basque Public Health System, including socio-demographic data, personal history, month and year of consultation, pneumococcal and meningococcal vaccination status, duration of fever, associated symptoms, maximum temperature, previous consultation in the ED, appearance upon arrival, physical exam, performed tests, microorganism isolated, final diagnosis, disposition and evolution of the patient. We included these data in the registry of IBI in the month after the visit to the ED.

For the purpose of this subanalysis, we included those children classified as previously healthy patients and excluded those non-previously healthy: immunosuppression (oncological illness, chronic renal failure, transplant patient, sickle cell disease); presence of a mechanical device (indwelling catheter, ventriculoperitoneal shunt, auditory prostheses); and chronic diseases/severe malformative syndromes.

2.1. Definitions

Invasive bacterial infection (IBI): isolation in blood or cerebrospinal fluid (CSF) of a bacterial pathogen, using bacterial culture or real time polymerase chain reaction (PCR) technique to detect *S. pneumoniae* and *N. meningitidis*.

Fever without a source (FWS): axillary or rectal temperature higher than 38 °C registered at home or in the ED, without associated respiratory symptoms, diarrhea process and findings on physical examination that allows identifying the source of the fever.

Occult bacteremia (OB): presence of a pathogenic bacterium in the blood of a well-appearing febrile child in the absence of an identifiable focus of infection.

Sepsis: based on the criteria published by Goldstein et al., with the following adjustment: well-appearing patients with fever and leukocytosis were not diagnosed with sepsis unless they had another added criterion (tachycardia, bradycardia, tachypnea or signs of organ dysfunction). [5]

Normal blood tests values: in accordance with the most accepted limits, we considered the following normal values: WBC between 5000 and 15,000/mm^3, ANC between 1500 and 10,000/mm^3, CRP less than 20 mg/L, PCT less than 0.5 ng/mL.

Well-appearing patients: patients with a stable pediatric assessment triangle [6] upon arrival at the ED.

2.2. Statistical analysis

We performed the statistical analysis using the IBM SPSS Statistics for Windows, version 23.0 (IBM, Armonk, New York, USA).

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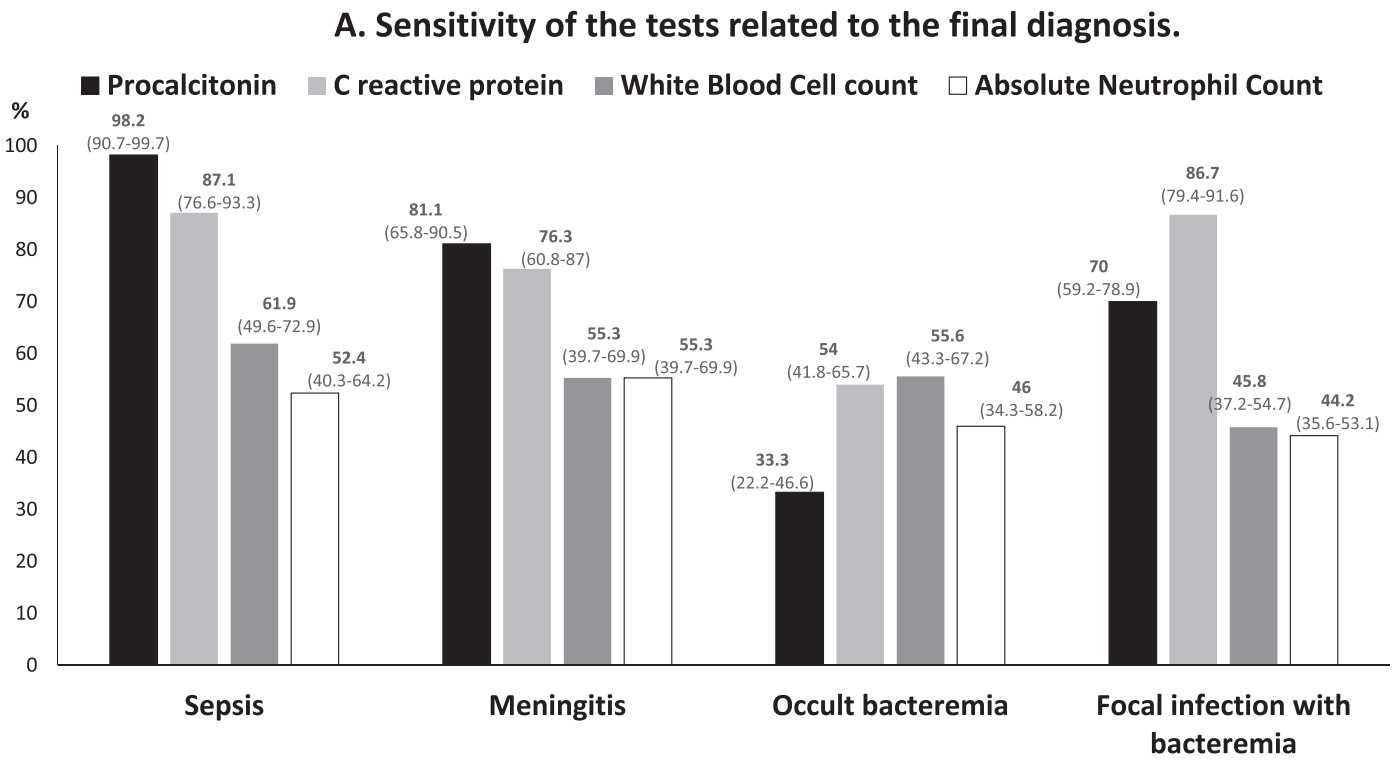

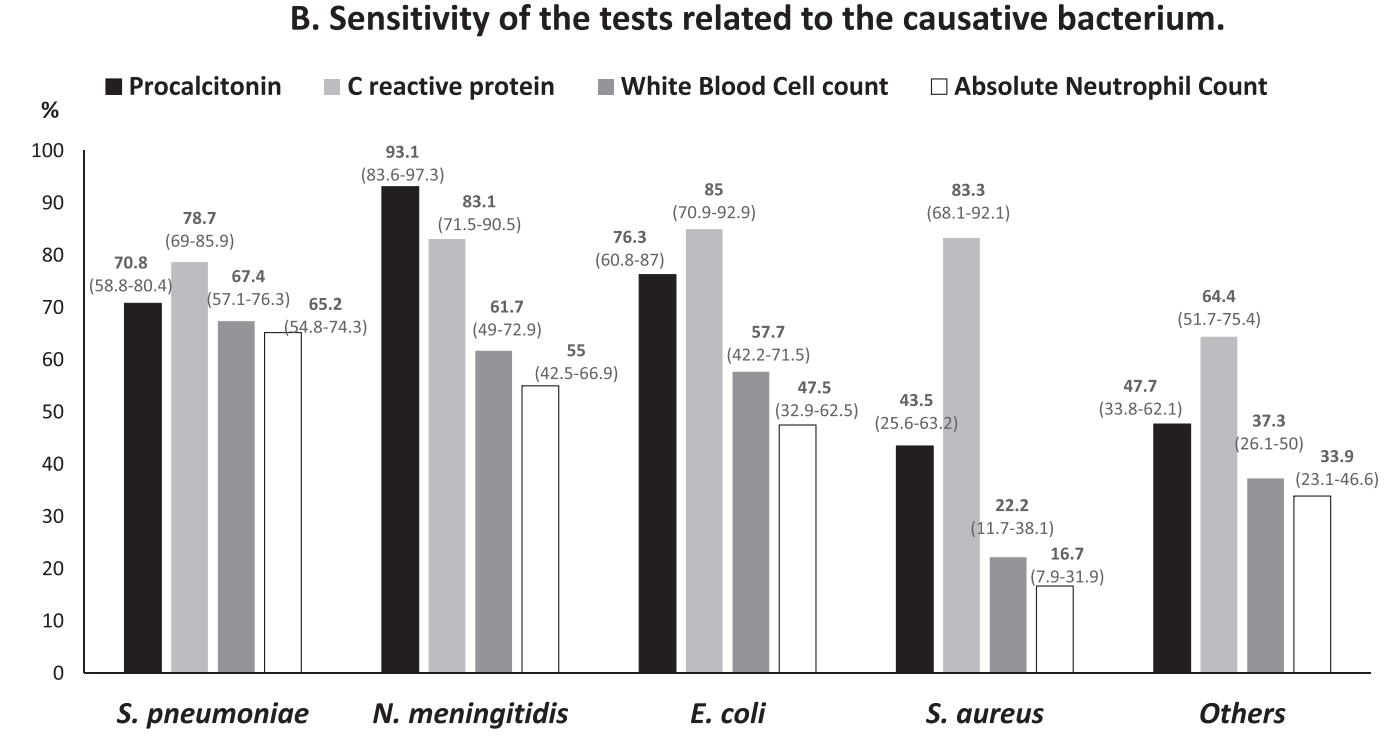

Rate of patients with procalcitonin >0.5 ng/mL, C reactive protein>20 mg/L, white blood cell count less than 5000 or higher than 15000/mm^3; absolute Neutrophil Count less than 1,500 or higher than 10,000/mm^3. 95% Confidence intervals in brackets.

Fig. 1. Profile of white blood cell count, absolute neutrophil count, C-reactive protein and procalcitonin in invasive bacterial infections.

We calculated the sensitivity of each blood test commonly used in the ED (WBC, ANC, CRP and PCT) for identifying an IBI. To identify variations in the markers' profile of each IBI and according to the causing bacterium, we also calculated the sensitivity of aforementioned markers for the different IBIs diagnosed.

The Clinical Research Ethics Committee of the Hospital approved the study (Code E11/52).

3. Results

During the study period, we registered 665.997 episodes in the pediatric ED, of which 367 (0.05%) were finally diagnosed with an IBI. Of these, 286 (77.9%) were previously healthy and were included in the study. One hundred and sixty (55.9%) were male, median age was 14 months (interquartile range 5–42), 107 (37.4%) had received two or more doses of pneumococcal conjugated vaccine (PCV) and 8 (2.8%) B meningococcal vaccine. Two hundred (69.9%) were well appearing and, of these, 95 had a normal physical exam. Final diagnoses were sepsis 64 (22.4%), meningitis 38 (13.3%), OB 63 (22.0%), focal infection with bacteremia 121 (42.3%) (respiratory tract infection 46, urinary tract infection 33, osteoarticular or soft tissue infection 33, and others 9). Isolated bacteria were *Streptococcus pneumoniae* 89 (31.1%), *Neisseria meningitidis* 61 (21.3%), *Escherichia coli* 40 (14.0%), *Staphylococcus aureus* 36 (12.6%), others 60 (21.0%). Two hundred and ten patients (73.4%) received antibiotics on the first visit to the ED, 3 died and 14 showed sequelae.

WBC and ANC were performed in 284 patients (99.3%), CRP in 283 (99.0%) and PCT in 228 (79.7%). Most patients without PCT were attended in the first two years of the study (phase of introduction of the PCT in our department) or were diagnosed with a pneumonia. Overall, 265 (92.7%) had, at least, one altered test. The sensitivity of each test was as follows: PCT 70.1% (CI 95% 63.9–76.0), CRP 78.1% (CI 95% 72.9–82.5), WBC 52.8% (CI 95% 47.0–58.6) and ANC 47.9% (CI 95% 42.1–53.7). Additionally, 85.2% (CI 95% 78.7–90) of the altered WBC count were leukocytosis and 99.5% (CI 95% 97.1–100) of the altered ANC were neutrophilia. Leukopenia was an uncommon finding except in patients with sepsis [22.2% (95% CI 13.7–33.9)].

The sensitivity of the blood tests varied related with the final diagnosis and the causing bacterium (Fig. 1).

Among those 89 patients in whom *S. pneumoniae* was isolated, 40 (44.9%) received at least two doses of pneumococcal conjugated vaccine. The accuracy of the markers did not vary related to the vaccination status. Twenty-nine febrile infants between 3 and 24 months of age were diagnosed with a pneumococcal OB. Of these, sensitivity of each marker was: PCT 43.5% (CI 95% 25.6–63.2); CRP 48.3% (CI 95% 31.4–65.6); WBC count 75.9% (CI 95% 57.8–87.8); ANC 58.6% (CI 95% 40.7–74.5).

Overall, 21 patients (7.3%) showed no alteration of any blood test. The median of age of these patients was 2 months (IQR 1–11 months) and, except for two, all of them were well-appearing. Final diagnosis were occult bacteremia 11 (52.4%), meningitis 4 (19%), and other focal infections 6 (28.6%). Six (28.6%) were started on antibiotics despite normal values of the blood tests (vs 242 of 261 patients, 92.7% of those with at least, one altered blood test; $p < 0.001$). All of them did well.

Globally, seventy-six patients (26.6%) had a previous visit to the ED and antibiotics were not started on that visit. Except for two, all of them were well-appearing on the first visit, median age and sex distribution was similar to the whole sample and most common diagnoses were fever without a source or upper respiratory tract infection (56, 73.7%). Two of these patients finally died and eight had sequelae (mainly neurological and osteoarticular sequelae).

4. Discussion

Most previously healthy febrile children with a microbiologically confirmed IBI show alterations of, at least, one of the blood tests commonly used in the ED. Nevertheless, it should be noted that the sensitivity of these markers varied related to the isolated causative bacterium and the final diagnosis of the patient. Overall, PCT and CRP appear more frequently altered than classic markers, mainly in children with severe disease like sepsis or meningitis, being their performance quite poor in children with occult bacteremia.

Identifying febrile children with an IBI when evaluated at the ED remains challenging and, initially, depends on recognizing clinical signs and symptoms. Most algorithms are based on abnormal selected vital parameters and level of consciousness. But, in a large proportion of children with fever due to self-limiting infections vital signs may be abnormal [7]. In addition, children are often able to maintain normal haemodynamic parameters in the early stages of sepsis. Thus, it is comprehensible to use blood tests in some situations to rule in or rule out an IBI.

In recent decades, new biomarkers, such as CRP and PCT, have been added to screening tests in febrile children. Our results confirm that, globally, CRP and PCT levels provide the most diagnostic value in feverish children to detect those with serious bacterial infection [3]. Furthermore, PCT offers some advantages in order to identify patients with IBI [8], including meningitis [9] and invasive meningococcal disease. CRP appears more useful when evaluating children with suspected focal infections with associated bacteremia, mainly soft tissue and osteoarticular infections due to *Staphylococcus aureus*. Children with occult bacteremia deserve special attention. These infants appear well and lack an identifiable focal bacterial source of infection. PCT is not very useful when evaluating febrile infants at risk for pneumococcal OB as it has previously been reported with CRP [10]. In these children, the sensitivity of classic markers, mainly WBC, is higher.

Finally, it should be underlined that adding more blood tests when evaluating febrile children may increase the number of patients who receive antibiotics instead of selecting better those who should receive them [11].

Our study has certain limitations. The data were collected retrospectively. Even so, all patients admitted in our pediatric ED are recorded electronically, including medical histories and notes concerning progression and follow-up of them. This makes the collection process consistent. On the other hand, this was not a multicenter study and, therefore, our results should be cautiously extrapolated to other settings. Finally, those febrile children with no identified pathogen in blood or CSF were not included in the study. This should have let us establishing the specificity and the predictive values of the different blood tests, providing a better accuracy of blood tests when evaluating these children in the ED.

Most previously healthy febrile children with an IBI show alterations of blood tests commonly obtained when evaluated in the ED. The response of these tests varies related to the isolated causative bacterium and the final diagnosis. This should be considered when tests are used to guide initial clinical decision-making in certain clinical scenarios.

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Ethics

Approved by The Clinical Research Ethics Committee of the Basque Country (internal code E11/52).

Author statement

Dr. Gangoiti conceptualized and designed the study, supervised data collection, analyzed the data, wrote the initial draft of the manuscript, and approved the final manuscript as submitted.

Dr. Fernandez collaborated in the design of the data collection system and critically revised the manuscript.

Dr. Gallego collaborated in the design of the study and critically revised the manuscript.

Dr. Gomez collaborated in the design of the study and critically revised the manuscript.

Dr. Benito reviewed the design of study and critically revised the manuscript.

Dr. Mintegi collaborated in the design of the study, supervised data collection, analyzed the data, revised the initial draft of the manuscript, and approved the final manuscript as submitted.

All of them approved the final manuscript as submitted.

Declaration of competing interest

The authors have no conflicts of interest to disclose.

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DISCUSSION

Several studies describe the effect of coronavirus disease in gastrointestinal system. Liver damage, expressed as elevation in liver aminotransferase levels, has been reported and diverse pathophysiologic mechanism has been proposed. Severe disease has been associated with higher rates of liver dysfunction.[1–3]

Prevalence rates of preexisting liver disease in COVID-19 adult patients vary from 3% to 11%. However, in pediatric population liver disease is rare. Several studies have identified significant risk factors for the severity of COVID-19 disease. Moreover, drug hepatotoxicity has been reported as a cause of liver impairment in patients with COVID-19. Many of the medications used for SARS-CoV-2 infection, such as antivirals, antibiotics, acetaminophen, and nonsteroidal anti-inflammatory drugs, are potentially hepatotoxic.[4] In critically ill COVID-19 patients, hepatic injury may be caused by changes in hemodynamics and oxygen delivery. In acute cardiovascular or respiratory failure, systemic arterial pressure suddenly declines, leading to a reduction in hepatic arterial perfusion, and hepatocellular hypoxia. Hypoxic hepatitis is associated with a sharp increase in LFTs.

SARS-CoV-2 engages the angiotensin-converting enzyme 2 as the entry receptor on host cells and uses the transmembrane protease serine 2 (TMPRSS2) for S protein priming.[5] Significant enrichment of angiotensin-converting enzyme 2 expression has been found in a major portion of the cholangiocytes and lower in hepatocytes, providing a theoretical basis for liver injury in COVID-19 infection. In addition to this, pathologic studies have illustrated the presence of the SARS-CoV-2 in postmortem liver biopsies of COVID-19 patients with liver enzyme abnormalities, contrary to previous studies that did not manage to identify the virus in liver tissue.[6] Wang et al demonstrated the presence of amounts of typical coronavirus particles in cytoplasm of hepatocytes in 2 patients.[7] The above support the hypothesis of direct SARS-CoV-2 infection in the liver, causing cytopathy of hepatocytes and impaired liver function.

Our 5-year-old patient was a previously healthy child, who had been heavily exposed to SARS-CoV-2. Preexisting liver disease or other comorbidities were absent. He had not been exposed to medications, before admission to pediatric department or during his hospitalization, remaining hemodynamically stable. His clinical phenotype with nausea and vomiting, in conduction with increased LFTs and inflammatory markers, in the absence of the above risk factors, supports the infectious cause of liver injury. The course of his disease was short, and the patient had a complete clinical recovery, with normalization of laboratory profile.

False negative results of RT-PCR testing for SARS-CoV-2 have been reported in several previous studies. A systematic review that included 34 studies, enrolling 12.057 COVID-19 patients, reported 1060 cases with RT-PCR negative findings in their initial assessment.[8] In the same article is stated that up to 54% of COVID-19 patients may have an initial negative RT-PCR result. Xiao et al found that 23.3% of 301 patients who had 3 consecutive SARS-CoV-2 RT-PCR assays in first 2 tests they had negative results. The median period between onset of symptoms and positive SARS-CoV-2 RT-PCR test result was 16 days (IQR, 10–23).[9] Another study that Yafang Li et al conducted, including 610 hospitalized patients from Wuhan, demonstrated that in the first test, 63.0% of COVID-19 were negative. Among them, in the second test, 72.9% remained negative. Among the patients with initial nonpositive results, 7 patients were eventually confirmed with COVID-19 by 3 repeated swab PCR tests, 4 were confirmed by 4 repeated tests, and 1 was confirmed by 5 repeated tests.[10] Our patient had been subjected to SARS-CoV-2 RT-PCR test with specimens from nasal swabs twice, initially at symptoms onset and later on the 9th day of the disease, and the results were negative in both of the tests. On the 16th day of the disease, he was tested for SARS-CoV-2 IgG antibodies with positive results in high titer.

CONCLUSION

The case details an unusual presentation of COVID-19 disease in children. The patient presented a mild clinical phenotype of the disease, affecting the gastrointestinal system, but greatly elevated liver enzymes, indicative of severe liver injure that was directly attributed to SARS-CoV-2. Although favorable prognosis of COVID-19 infection in children has been reported in many studies, clinicians need to be aware of this disease expression to ensure prompt recognition.

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REPEATED EMERGENCY DEPARTMENT VISITS AMONG CHILDREN WITH INVASIVE BACTERIAL INFECTIONS

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Abstract: We carried out a retrospective cohort study of 271 previously healthy children younger than 14 years old diagnosed with invasive bacterial infection in an emergency department. Of them, 72 (26.6%) had previous visits to the emergency department. Not identifying children with an invasive bacterial infection and not administering antibiotics on the first visit was associated with a severe outcome.

Key Words: antibiotic treatment, invasive infection, outcome, revisit

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Fever is one of the main reasons for consultation among children attending the emergency department (ED). Most cases correspond to self-limiting viral infections. The rate of invasive bacterial infections (IBIs) has declined significantly after the introduction of the conjugate vaccines. However, they are still a major cause of death in developed countries.[1]

Early identification of children with IBI may be difficult. Children are often brought to the ED after only a few hours of fever and children with an IBI can be difficult to distinguish from those with self-limited febrile illnesses. In addition, most children with IBI are younger than 2–3 years old, and in these patients, the manifestations of many infectious diseases are usually unspecific.[2] In a recent study, 22% of children with bacterial meningitis or sepsis had repeated ED visits before admission, yet they had health outcomes similar to those of children admitted on initial visit.[3] Nevertheless, pediatric sepsis management guidelines recommend administration of intravenous antimicrobials be initiated as soon as possible after recognition and within 1 hour for both sepsis and septic shock.[4] In a previous article,[5] we identified duration of fever less than 24 hours, symptoms other than fever and not being well-appearing upon arrival to the ED to be independent risk factors for greater severity. Nevertheless, previous ED visits were not considered.

We hypothesize that not administering parenteral antibiotics on the initial visit to the ED is related to severe outcome in pediatric IBIs.

The objective of the study was to evaluate the impact of not administering parenteral antibiotics on initial visit to the ED on the outcome of children with an IBI.

PATIENTS AND METHODS

We conducted a retrospective registry-based cohort study that included all the previously healthy children less than 14 years old diagnosed with an IBI in a pediatric ED between 2008 and 2019. Our ED is a tertiary teaching hospital with around 55,000 episodes/year corresponding to children younger than 14 years of age.

Definitions

IBI is defined as the identification of bacterial pathogen in blood and/or cerebrospinal fluid by growth in bacterial culture and/or genomic detection of *Neisseria meningitidis* or *Streptococcus pneumoniae* by real-time quantitative polymerase chain reaction (q-PCR) technique.

Severe outcome is defined as patient who died or had permanent sequelae identified in the following 12 months after the IBI. Sequelae were defined as a morbid condition following or occurring as a consequence of the IBI.

Well-appearing patients are defined as those with a stable pediatric assessment triangle upon arrival at the ED.

Nonpreviously healthy patients are those with immunosuppression (oncological illness, chronic renal failure, transplant patient, sickle cell disease); presence of a mechanical device (indwelling catheter, ventriculoperitoneal shunt, auditory prostheses) and chronic diseases/severe malformative syndromes.

Sepsis is defined as that based on the criteria published by Goldstein et al,[6] with the following adjustment: well-appearing patients with fever and leukocytosis were not diagnosed with sepsis unless they had another added criteria (tachycardia, bradycardia, tachypnea or signs of organ dysfunction).

Meningitis is defined as the identification of bacterial pathogen in cerebrospinal fluid by growth in bacterial culture and/or genomic detection of *N. meningitidis* or *S. pneumoniae* by q-PCR technique; or pleocytosis with identification of bacterial pathogen in blood by culture or q-PCR technique.

Patient Identification

Patients with IBI were identified from the hospital's electronic records as it has been previously described.[5] Sequelae were addressed reviewing medical electronic records of the children in the following 12 months after the IBI.

Nonpreviously healthy patients were excluded.

We carried out the statistical analysis using the statistical program IBM SPSS Statistics for Windows Version 23.0 (Armonk, NY). The qualitative variables were described using absolute frequencies and percentages, and the continuous variables were described using both the mean and standard deviation or median and interquartile range. The χ^2 test was used to study the association between qualitative variables.

The Clinical Research Ethics Committee of the Hospital approved the study (Code E11/52).

RESULTS

During the study period, we registered 601,902 episodes in the ED, corresponding to children less than 14 years old. Of these, 342 were diagnosed with an IBI. Seventy-one were excluded. Seventy (20.5%) were not previously healthy: immunosuppression (41; 12%), mechanical device (15; 4.4%) chronic diseases or complex syndromes (14; 4.1%). Another one was excluded because he died before reaching the ED (sepsis due to *S. pyogenes*).

Finally, we included 271 previously healthy children less than 14 years old diagnosed with an IBI. Median age was 15 months old (interquartile range 5–43 months old; of them 18 younger than 1-month-old and 34 between 1 and 3 months of age) and 118 (43.5%) were female. One-hundred ninety-nine patients (73.4%) received parenteral antibiotic on first visit and 72 (26.6%) did not (Table 1). Median of time between the first and second visit in those patients who did not receive parenteral antibiotic was 36 hours (interquartile range 24–48 hours). Fifteen patients had severe outcome, including 3 deaths and 12 patients who developed sequelae: neurologic 5 (replacement of ventriculoperitoneal device, hydrocephalus, deafness and epilepsy), 3 osteoarticular (need for a prosthesis, permanent limp and small amputations), 2 chronic renal failure (one of them requiring kidney transplant), 2 chronic restrictive respiratory problems and 1 cardiologic sequelae (multiple valve replacements). Seven of the 15 patients with severe outcome did not receive antibiotic on the first visit (2 deaths, 5 sequelae).

The rate of severe outcome varied related to the type of IBI: sepsis 9 of 61 (14.8%; 95% confidence interval [CI], 7–26.2), meningitis 3 of 36 (8.3%; 95% CI, 1.7–22.5), occult bacteremia 0 and focal infection with bacteremia 3 of 119 (2.5%; 95% CI, 0.5–7.2). The rate of severe outcome did not vary related to the time interval between the initial and return visit (3 of the 29 children who had an ED visit in the preceding 24 hours had severe outcome, 10.3%; vs 4 of the 40 children who returned to the ED within more than 24 hours, 10%, $P = 1$).

TABLE 1. Characteristics of Previously Healthy Patients With an Invasive Bacterial Infection in Relation to the Administration or Nonadministration of Parenteral Antibiotic on the First Visit to the Emergency Department

Characteristics	Parenteral Antibiotic Administered in the First ED Visit		
	Yes (n = 199)	No (n = 72)	*P*
Age (mo)	15 (5–43)	14 (4–42)	NS
Sex (female)	87 (43.7%)	31 (43.1%)	NS
Season			<0.01
Spring	33 (16.6%)	21 (29.2%)	
Summer	31 (15.6%)	16 (22.2%)	
Autumn	68 (34.2%)	19 (26.4%)	
Winter	67 (34.2%)	16 (22.2%)	
Fever: yes	195 (98%)	59 (81.9%)	<0.01
Duration of fever (h)	12 (5–32)	12 (8–48)	NS
Not well-appearing upon the arrival to the ED	56 (28.1%)	2 (2.8%)	<0.01
No other symptom except fever	58 (29.1%)	33 (45.9%)	0.01
Digestive	44 (22.1%)	11 (15.3%)	
Respiratory tract and ORL	37 (18.6%)	18 (25%)	
Neurological	37 (18.6%)	3 (4.2%)	
Exanthema	22 (11.1%)	2 (2.8%)	
Joint/soft tissue	17 (8.5%)	7 (9.7%)	
Normal physical examination	72 (36.2%)	51 (70.8%)	<0.01
Other signs			
Exanthema	50 (25.1%)	6 (8.3%)	
Neurological	38 (19.1%)	2 (2.8%)	
Respiratory tract and ORL	28 (14.1%)	11 (15.3%)	
Joint/soft tissue	17 (8.5%)	2 (2.8%)	
Isolated microorganism			NS
Streptococcus pneumoniae	60 (30.2%)	24 (33.3%)	
Neisseria meningitidis	47 (23.6%)	10 (13.9%)	
Staphylococcus aureus	20 (10.1%)	14 (19.4%)	
Escherichia coli	31 (15.5%)	7 (9.7%)	
S. agalactiae	11 (5.5%)	1 (1.4%)	
Others	30 (15.1%)	17 (22.3%)	
Final diagnosis			NS
Sepsis	47 (23.6%)	14 (19.4%)	
Meningitis	28 (14.1%)	8 (11.1%)	
Occult bacteremia	36 (18.1%)	19 (26.4%)	
Focal infection with bacteremia	88 (44.2%)	31 (43.1%)	
Urinary tract infection	28 (14.1%)	4 (5.6%)	
Pneumonia	24 (12.1%)	8 (11.1%)	
Osteoarticular or soft tissue infection	19 (9.5%)	12 (16.7%	
Others	17 (8.5%)	7 (9.7%)	
Severe outcome	8 (4%)	7 (9.7%)	0.07

NS indicates not significant; ORL, otorhinolaryngological.

Data expressed as n (%) except for age and duration of fever (median and interquartile range).

DISCUSSION

A significant percentage of previously healthy children with an IBI are not identified on their first visit to the ED. Failure to identify IBI and not initiating antibiotic on first visit is associated with higher mortality and sequelae rate. Nearly half of the patients with severe outcome had previously visited the ED and were managed as outpatients without antibiotics.

In our study, around a quarter of children with an IBI had previous ED visit before admission, similar to previously published in children with more severe IBIs, such as sepsis and/or meningitis.[3] In that previous study,[3] children with bacterial meningitis or sepsis with repeated ED visits before admission had health outcomes similar to those of children admitted on initial visit. It was argued that both sepsis and meningitis were probably not present at the first visit, not being possible to be diagnosed.[7] This is quite controversial. Recommendations on the management of children with IBIs, and specifically with sepsis, underline the importance of early recognition and considering sepsis in all children with signs or symptoms that indicate possible infection and that delays in the administration of antibiotics worsen outcomes of sepsis and meningitis.[8] In addition, currently, children are brought very promptly to the ED. In a recent study, the median of the duration of the fever in infants younger than 3 months was 2 hours.[9] Such an early consultation may alter the performance of the physical examination to identify patients to be tested for IBI. In our series, no tests were performed on around two-thirds of children not diagnosed on first visit. A sepsis screening tool should be included in a recognition bundle to aid clinicians evaluating children with possible sepsis. For these tools to be effective, all children presenting to the ED should be screened for sepsis and most tools emphasize the use of clinical parameters rather than laboratory tests.[10] However, many febrile children have warning signs of sepsis, but the large majority have nonlife-threatening infections.

The main limitation of our study is that it is a unicenter study, so the conclusions must be cautiously extrapolated to other settings. Although, we consider that results are similar in other pediatric ED of developed countries. This was also a retrospective study being challenging to assess whether clear overall clinical signs were present at the first visit. Nevertheless, all the episodes of our ED are registered electronically making easier to obtain the data in the following month after the visit, although some important items as vital signs were not recorded in all the patients, and it was not possible to analyze them. This reflects a common problem of the pediatric EDs. Finally, sample size limits the ability to do a specific analysis of the sepsis and meningitis. Although, the percentage of children with sepsis and/or meningitis not diagnosed on first visit was similar to that of all IBIs.

Not identifying children with an IBI and not administering antibiotics on the first visit to the ED is associated with a severe outcome. Best practices need to be identified for the early identification and prompt antibiotic administration in children with IBI.

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Late-onset Group B *Streptococcus* Bacteremia Evaluated in the Pediatric Emergency Department and Risk Factors for Severe Infection

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Background: To describe the infants presenting to pediatric emergency departments (PEDs) and diagnosed with group B *Streptococcus* (GBS) late-onset disease (LOD) bacteremia and identify risk factors for severe infection and pediatric intensive care unit (PICU) admission.

Methods: Observational study and subanalysis of a multicenter prospective registry. Setting: pediatric emergency department. Inclusion criteria: infants between 7 and 89 days of age with positive blood culture for GBS seen between 2011 and 2016 at any of 22 Spanish PEDs. Main outcome: risk factors (clinical and laboratory variables) for severe infection (sepsis/septic shock or meningitis) and PICU admission. Second, the prevalence of poor outcomes (acute complications, sequelae or death).

Results: Among 118 patients with LOD, 74 (62.7%) presented a severe infection: 66 sepsis/septic shock (11 with associated meningitis) and 8 meningitis. Thirty-five patients (29.7%) were admitted to a PICU. An altered Pediatric Assessment Triangle (PAT) upon arrival and leukopenia were the only independent risk factors for severe infection [odds ratio (OR): 43.6; 95% confidence interval (CI): 8.1–235.7, $P < 0.01$] and PICU admission (OR: 11.6; 95% CI: 1.5–91.4; $P < 0.019$), respectively. Six patients (5.1%) developed a poor outcome, including 2 deaths (1.7%); all had an altered PAT, elevated procalcitonin (range 4.7–100 ng/ml), and were diagnosed with sepsis/septic shock and admitted to a PICU. Four developed leukopenia.

Conclusions: Infants with GBS LOD frequently develop sepsis/septic shock and bacterial meningitis, associated with non-negligible morbidity and mortality. Clinical appearance was the only risk factor for severe infection, whereas leukopenia was related to PICU admission.

Key Words: bacteremia, children, *Streptococcus agalactiae*, emergency department, sepsis

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INTRODUCTION

Group B *Streptococcus* (GBS) is the second most frequent cause of invasive bacterial infection (IBI) among febrile infants younger than 3 months of age, behind *Escherichia coli*, and it is the leading cause of sepsis and bacterial meningitis in this population.[1–3] GBS infection in these infants is classified into early-onset disease (EOD: neonates 1–6 days old) and late-onset disease (LOD: infants 7–89 days old). The incidence of EOD has declined with the introduction of universal screening of pregnant women for GBS colonization and with the widespread use of intrapartum antibiotic prophylaxis (IAP).[4,5] However, IAP has not been shown to be effective in decreasing LOD;[4,6] in fact, in developed countries where IAP is used for prevention, the relative proportion of EOD and LOD is changing[4] in favor of LOD-GBS disease.

Although GBS is a known cause of bacteremia in febrile infants between the ages of 7 and 89 days, to our knowledge no large series have analyzed GBS infections in pediatric emergency departments (PEDs) for this age group.

The main objective of this study was to describe the epidemiologic and clinical features and laboratory results of infants presenting to participating PEDs and diagnosed with LOD-GBS bacteremia. As a secondary objective, we sought to identify risk factors for severe infection and pediatric intensive care unit (PICU) admission in these patients.

MATERIALS AND METHODS

Database

We performed a secondary analysis of a large, multicenter, cross-sectional prospective registry created in 2010 by the Spanish Society of Pediatric Emergency Medicine and comprising positive blood cultures (BC) obtained in 22 PEDs between 2011 and 2016.

The methodology applied and the BC technique were explained in the parental study.[7] To perform the current secondary analysis, we included infants from the registry between the ages of 7 and 89 days with GBS-related bacteremia.

Data Collection

Data were collected through a standardized online form, which included age, sex, risk factors for EOD GBS, Pediatric Assessment Triangle (PAT) on arrival at the PED, duration and degree of fever, other associated symptoms, physical examination (PE) findings, results of laboratory tests, diagnosis, management and outcome. Medical records were reviewed for all patients, and the parents or caregivers of the infants received a follow-up telephone call within 1 month after the initial visit to the PED to collect further data on the course of the episode.

Definitions

LOD: GBS infection in infants 7–89 days old.

Risk factors for EOD GBS infection included maternal GBS colonization or unknown status and delivery at <37 weeks of gestation.

The PAT was used to assess the overall initial impression of the child. The PAT is a tool used to evaluate appearance, work of breathing, and circulation to skin by using specific and predefined

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physical, visual and auditory findings. If any of these 3 components was abnormal, the patient was considered unstable.

PE was considered to be altered if any findings related to the infectious process were in evidence.

GBS occult bacteremia (OB): isolation of GBS in the blood of a well-appearing febrile infant in the absence of an identifiable focus of infection.

Sepsis: based on the criteria published by Goldstein et al.[8] If a patient presented persistent hypotension and needed vasopressors despite adequate fluid resuscitation, they were diagnosed with septic shock.

Meningitis: isolation of a bacterial pathogen from a cerebrospinal fluid (CSF) culture, detection of a bacterial pathogen in the CSF by molecular methods or isolation of bacteria from BC in a patient with CSF pleocytosis.

Severe LOD-GBS: sepsis/septic shock, meningitis and sepsis/septic shock with associated meningitis.

Poor outcome: acute complications, sequelae or death.

Blood test values considered normal were as follows: white blood cell count (WBC) 5000–15,000/mm^3, absolute neutrophil count (ANC) 1500–10,000/mm^3, C-reactive protein (CRP) <20 mg/L and procalcitonin (PCT) <0.5 ng/ml.

Analysis

Data normality was determined by calculating skewness in relation to standard error values. Normally distributed data were expressed as mean ± standard deviation (SD) and non-normally distributed data as the median and interquartile range (IQR). Two-tailed *t*-tests were used to compare mean values between groups for normally distributed data, and the Mann-Whitney U test was used for non-normally distributed data. Categorical variables are expressed as percentages and were compared using the chi-square test (or Fisher's exact test where expected values were <5 for >25% of cells or <1 for any cell). A *P*-value <0.05 was deemed statistically significant.

The sensitivity of each blood test in identifying GBS bacteremia overall and in distinguishing severe from nonsevere disease was calculated.

Baseline risk factors for severe infection and PICU admission were age, maximum temperature, EOD GBS infection risk factors, altered PAT upon arrival, altered PE upon arrival, WBC (categorized into 3 groups: <5000/mm^3, 5000–15,000/mm^3 and >15,000/mm^3), ANC (categorized into 3 groups: <1500/mm^3, 1500–10,000/mm^3 and >10,000/mm^3); CRP and PCT and were analyzed by means of binary logistic regression. As an exploratory test, backward stepwise regression (likelihood ratio) was performed for those binary variables with a *P*-value <0.2 on univariate analysis. Statistical analyses were performed using STATA v.15.

This study was approved by the Ethics Committee of the Basque Country (approval number PI2011040). Approval for the study and for the sharing of data with the coordinating institution and with the centralized data center was granted by the institutional review board of each participating institution.

RESULTS

Between 2011 and 2016, we recorded 3,936,827 PED episodes and obtained 1696 bacterial isolates in BC [0.04%; 95% confidence interval (CI): 0.04–0.05]. GBS grew in 134 (7.9%, CI: 6.6–9.2) of these cultures, 118 from infants (88.1 %) with LOD (Fig. 1). Table 1 contains the epidemiological and clinical data of these 118 infants.

Seventeen (14.4%) patients with LOD had at least one EOD GBS risk factor: 10 infants with maternal GBS colonization or unknown colonization status, 5 preterm infants and 2 infants with

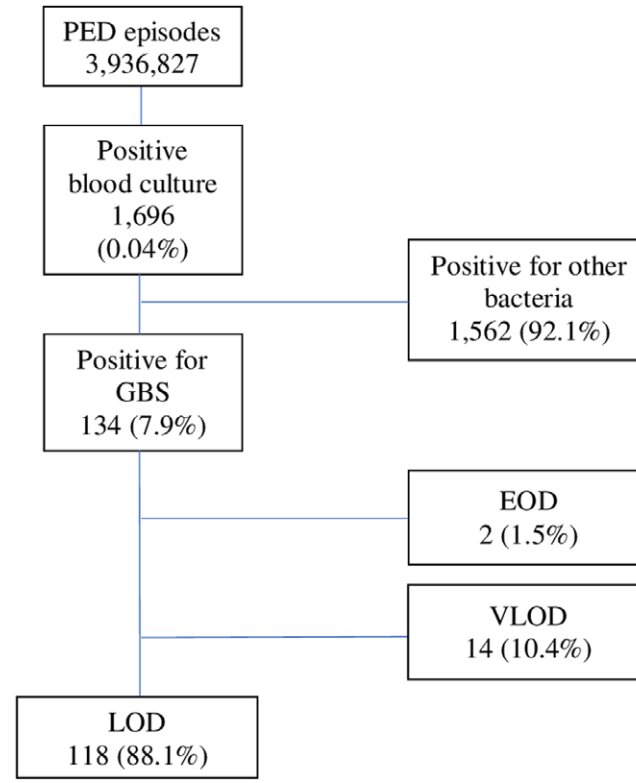

FIGURE 1. Flow-chart indicating included and excluded patients. EOD, early-onset disease; GBS, group B *Streptococcus*; LOD, late-onset disease; PED, pediatric emergency department; VLOD, very late-onset disease. full color online

Table 1. Epidemiologic and clinical features, management, and outcomes of infants with late-onset disease Group B *Streptococcus*

	Late-onset disease (N = 118)
Sex (males), n (%)	68 (57.6)
Age–days, median (IQR)	28 (16–43)
Normal PAT upon arrival, n (%)	56 (47.5)
Reported symptoms, n (%)	
Fever	86 (72.9)
Fever without a source	29 (24,6)
Fever with other symptoms	57 (48.3)
Irritability	38 (32.2)
Somnolence, lethargy	20 (16.9)
Respiratory symptoms	13 (11.0)
Others*	16 (13.6)
Fever, timesince onset–hours, median,(IQR)	2 (0-4)
Normal PE, n (%)	56 (47.5)
Discharge to home, n (%)	3 (2.5)
Admission, n (%)	
Ward	80 (67.8)
PICU	35 (29.7)
Outcomes, n (%)	
Acute complications	6 (5.1)
Sequelae	2 (1.7)
Death	2 (1.7)

*Digestive, local pain.

CI indicates confidence interval; IQR, interquartile range; PAT, Pediatric Assessment Triangle; PE, physical examination; PICU, pediatric intensive care unit.

both risk factors. Two preterm infants with unknown maternal GBS status did not receive IAP; both were diagnosed with sepsis and required PICU admission.

Regarding laboratory findings, WBC and ANC were performed in all patients, CRP was measured in 117 (99.2%) and PCT in 93 (78.8%). Overall, 91 (77.1%) had at least one altered test. The sensitivity of each test was as follows: PCT 80.6% (95% CI: 71.1–88.1), WBC 44.1% (95% CI: 34.9–53.5), ANC 34.7% (95% CI: 26.2–44.1) and CRP 27.4% (95% CI: 19.5–36.4). The sensitivity of the blood tests for diagnosing severe infections is shown in Table 2.

The final diagnosis was sepsis/septic shock in 66 patients (55.9%, 11 with associated meningitis), OB in 40 (33.9%), meningitis in 8 (6.8%) and focal infection in 4 infants [3.4%, 2 osteoarticular and 2 urinary tract infection (UTI)]. Overall, 74 (62.7%) had a severe infection.

Among the patients with severe infection, 15 (20.3%) had normal PAT upon arrival: 7 were neonates younger than 21 days of age and 7 had abnormal values on blood tests. The remaining patient was a 26-day-old neonate diagnosed with cellulitis-adenitis and associated meningitis with normal values on blood tests and no findings of note on arrival to the PED.

From the multivariate model, the baseline risk factors associated with severe infection are shown in Table 3.

GBS was isolated in another location in 20 patients (16.9%): in CSF in 17 patients and in urine in 3 patients. Seven patients had a concomitant UTI caused by another bacterium and one patient had concomitant bacterial meningitis due to *E. coli*.

Admission was required in 115 patients, that is, 80 (67.8%) to the ward and 35 (29.7%) to the PICU. Three patients (2.5%) were discharged home (Table 1): a 35-day-old infant, another 39-day-old patient and another who was 52 days old; all had a normal PAT, normal blood values and were diagnosed with OB. None of the 3 developed a poor outcome.

Table 4 shows the baseline risk factors associated with PICU admission from the multivariate model.

Six (5.1%) patients presented a poor outcome, all of whom were neonates (range 9–26 days of life) with altered PAT, elevated PCT (range 4.7–100 ng/ml), diagnosed with sepsis/septic shock (2 with associated meningitis) and admitted to the PICU. Four had leukopenia (range 2300–9200 WBC/mm^3). All of them presented acute complications: seizures (2), cerebral candidiasis (1), disseminated intravascular coagulopathy (1), endocarditis (1) and pneumonia with pleural effusion (1). Two (1.7%) developed sequelae: one presented a pulmonary valve residual wart and another developed central diabetes insipidus and epileptic encephalopathy. Two patients died (1.7%), including a 12-day-old neonate whose mother was colonized by GBS and received IAP, and another, a 26-day-old infant with a premature (35 weeks) birth with an unknown state of mother's vaginal swab in whom IAP was not administered.

DISCUSSION

Almost two-thirds of the infants with GBS LOD bacteremia studied here presented a severe infection, and around 5% developed acute complications or sequelae, including a mortality rate of nearly 2%. Presenting an altered PAT on arrival to the PED was the only risk factor identified for a severe infection, and this factor also seems to be related to a poor outcome.

Our registry study is one of the largest prospective series analyzing GBS bloodstream infections in infants between the ages of 7 and 89 days. Preliminary data from the original study demonstrated that GBS was the second most common cause of bacteremia among febrile infants younger than 3 months behind *E. coli,*[7] as found in recent multicenter studies.[4,9,10] Compared with data published on *E. coli* bacteremia[11], GBS bloodstream infections are more severe and more frequently lead to sepsis/septic shock and meningitis.[12] Acute complications and deaths are also more frequent with GBS.

In our study, risk factors for EOD GBS infection were present in less than 20% of the infants with GBS LOD. Most of the infants 7–89 days old with a GBS bacteremia were previously healthy and presented no risk factors, thus contrasting with data from studies on EOD[4]. Our results support previous studies finding that IAP does not prevent GBS LOD[4,13] and that other strategies, such as the administration of multivalent vaccines in pregnant women should be considered.[14–16]

PAT alterations are the only independent risk factor for severe infection. An altered PAT should always be considered a risk factor for a poor outcome in pediatric patients. Even so, in our study, only one infant diagnosed with a severe GBS LOD

Table 2. Epidemiologic features, clinical characteristics, laboratory test results, and management with severe and nonsevere infections

	Nonsevere infection* (n = 44)	Severe infection† (n = 74)	*P*-value
Sex (males), n (%, 95% CI)	28 (63.6, 47.8–77.6)	40 (54.1, 42.1–65.7)	n.s.
Risk factors for GBS, n (%, 95% CI)	3 (6.8, 1.4–18.7)	14 (18.9, 10.7–29.7)	n.s.
Age – median days (IQR)	28.5 (16–42.5)	28 (15–43)	n.s.
Normal PAT upon arrival, n (%, 95% CI)	41 (93.2, 81.3–98.6)	15 (20.3, 11.8–31.2)	**<0.001**
Normal PE upon arrival, n (%, 95% CI)	31 (70.5, 54.8–83.2)	25 (33.8, 23.2–45.7)	**<0.001**
Admission			**<0.001**
Ward	37 (84.1, 69.9–93.4)	43 (58.1, 46.1–69.5)	
PICU	4 (9.1, 2.5–21.7)	31 (41.9, 30.5–53.9)	
WBC (median/mm^3, IQR)	11,840 (8300–16,455)	7,300 (4100–11,200)	**<0.001**
Sensitivity (WBC <5000 or >15,000/mcL)	38.6% (95% CI:24.4–54.5%)	35.1% (95% CI: 24.4–47.1%)	
ANC (median/mm^3,IQR)	6,310 (4500–10,598)	4,530 (1975–8,300)	**0.01**
Sensitivity (ANC <1500 or >10,000/mcL)	34.1% (95% CI: 20.5–49.9%)	35.1% (95% CI: 24.2–47.1%)	
CRP (median mg/L, IQR)	5.5 (2.1–18.0)	7.7 (3.6–24.0)	n.s.
Sensitivity (CRP ≥20 mg/L)	23.3% (95% CI: 11.8–38.6%)	29.7% (95% CI: 19.7–41.5%)	
PCT (median ng/ml, IQR)	1.7 (0.4–6.5)	3.5 (0.7–21.8)	n.s.
Sensitivity (PCT ≥0.5 ng/ml)	71.8% (95% CI: 55.1–85.0%)	87.0% (95% CI: 75.1–94.6%)	

*Included: occult bacteremia and focal infection (osteoarticular and urinary tract infection).

†Included: sepsis/septic shock, meningitis, and sepsis/septic shock with associated meningitis.

ANC indicates absolute neutrophil count; CI, confidence interval; CRP, C-reactive protein; GBS, Group B *Streptococcus*; n.s., not significant; PAT, Pediatric Assessment Triangle; PCT, procalcitonin; PE, physical examination; PICU, pediatric intensive care unit; WBC, white blood cell count.

Table 3. Multivariate analysis to identify independent risk factors for severe infection

Risk factors for severe infection	OR	95% CI	*P*-value
Age (days)	0.9	0.95–1.02	n.s.
Maximum temperature (ºC)	0.7	0.4–1.2	n.s.
Altered PAT upon arrival (%)	43.6	8.1–235.7	**<0.001**
Altered PE upon arrival (%)	1.5	0.3–6.9	n.s.
WBC (/mm^3)			
Group 1: <5000	1.5	0.05–45.3	n.s.
Group 2: 5000–15,000	Reference	Reference	
Group 3: >15,000	5.1	0.6–45.4	n.s.
ANC (/mm^3)			
Group 1: <1500	1.2	0.02–86.1	n.s.
Group 2: 1500–10,000	Reference	Reference	
Group 3: >10,000	0.2	0.02–2.3	n.s.
CRP (mg/L)	1.0	0.9–1.0	n.s.
PCT (ng/ml)	1.0	0.9–1.1	n.s.

ANC indicates absolute neutrophil count; CI confidence interval; CRP, C-reactive protein; n.s., not significant; OR, odds ratio; PAT, Pediatric Assessment Triangle; PCT, procalcitonin; PE, physical examination; WBC, white blood cell count.

Table 4. Multivariate analysis to identify independent risk factors for pediatric intensive care unit admission

Risk factors for PICU admission	OR	95% CI	*P*-value
Age (days)	0.9	0.9–1.0	n.s.
Maximum temperature (ºC)	1.0	0.3–3.9	n.s.
GBS infection risk factors (%)	1.4	0.3–6.7	n.s.
Altered PAT upon arrival (%)	7.1	0.9-56-5	n.s.
Altered PE upon arrival (%)	3.2	0.5–21.3	n.s.
WBC (/mm^3)			
Group 1: <5000	11.6	1.5–91.4	**0.019**
Group 2: 5000–15,000	Reference	Reference	
Group 3: >15,000	0.08	0.01–2.2	n.s.
ANC (/mm^3)			
Group 1: <1500	0.8	0.1–8.1	n.s.
Group 2: 1500–10,000	Reference	Reference	
Group 3: >10,000	7.0	0.3–156.7	n.s.
CRP (mg/L)	1.1	0.999–1.14	n.s.
PCT (ng/ml)	1.0	0.968–1.04	n.s.

ANC indicates absolute neutrophil count; CRP, C-reactive protein; CI, confidence interval; GBS, Group B *Streptococcus*; n.s., not significant; OR, odds ratio; PAT, Pediatric Assessment Triangle; PCT, procalcitonin; PE, physical examination; PICU, pediatric intensive care unit; WBC, white blood cell count.

had a normal PAT upon arrival to the PED, including 7 of the 10 patients with meningitis. This could be partially explained by the short history of symptoms at the time of PED assessment and by the young age of these infants, which makes it more difficult to properly implement the PAT. In fact, most infants in our sample were brought to the PED after only a few hours of fever (median 2 hours), and 11 of the 15 infants with a severe infection and normal PAT were neonates.

Clinical decisions regarding these infants should be supported by laboratory tests (blood, urine and CSF) in addition to PAT and PE to identify infants at high risk of IBI, as recommended by a majority of the validated approaches for febrile infants ≤90 days old.[17,18] PCT was the blood biomarker with the highest sensitivity (80.6% vs. 27.4% for CRP); indeed, PCT sensitivity was even higher for identifying a severe infection, while CRP sensitivity remained poor.[19,20] The short time between the symptom onset and presentation to the PED could explain this finding, since CRP is generally not detectable in serum until 12 hours after the onset of inflammation,[21] whereas PCT has a faster kinetic. With the exception of one 26-day-old neonate, all infants in our series with severe infections and normal PAT fulfilled the high-risk criteria for IBI, such as age under 21 days or abnormal analytical values,[18] and antibiotic therapy was administered in all cases. The aforementioned neonate did not develop a poor outcome.

Leukopenia was the only independent risk factor for PICU admission. Curiously, leukopenia in well-appearing infants was not found to be a risk factor for a poor outcome, thus contrasting with previous reports.[22,23]

On the one hand, a significant number of GBS colonizations were isolated in locations other than the blood (20, 16.9%), mainly CSF (17, 14.4%). This reaffirms the current recommendation to perform a lumbar puncture, if it has not been done before, when GBS bacteremia is identified in infants under 3 months of age.[24] GBS was also isolated concomitantly in urine, but much less frequently (2.5%), as reported in previous studies.[9] On the other hand, 8 (6.8%) other infants had a positive culture for other microorganisms, 7 in urine (3 UTI) and 1 CSF culture. All were Gram-negative microorganisms, which are the most common in these infants.[9]

Our study has certain limitations. First, it was not specifically designed to investigate GBS in patients with positive bloodstream culture. Not all known GBS risk factors have been considered in our registry, as only maternal GBS colonization or unknown status and delivery at <37 weeks of gestation have been reported. Second, although the same criteria were established to detect sepsis/septic shock, some infants may have been misclassified. Third, PICU admission did not follow the same criteria and may have varied from one hospital to another. Additionally, the indication for respiratory and hemodynamic support was also unknown. Nevertheless, we believe that the data collected allow us to characterize GBS LOD and may help to better identify these children in the PED, especially those with severe infection.

We conclude that infants with LOD due to GBS frequently develop sepsis/septic shock and bacterial meningitis with nonnegligible morbimortality, especially those infants with an altered PAT and leukopenia. Different prevention strategies are necessary for these infants.

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Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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CARTAS CIENTÍFICAS

Impacto de la pandemia de COVID-19 en las infecciones bacterianas invasivas en urgencias☆

Impact of the COVID-19 pandemic on pediatric invasive bacterial infections

Sra. Editora,

Durante la pandemia por el SARS-CoV-2 hubo una disminución de las consultas en los servicios de urgencias de pediatría (SUP) a nivel internacional[1]. Las medidas de protección adoptadas se acompañaron de una disminución de la incidencia de las infecciones bacterianas invasivas (IBI) transmitidas por vía respiratoria, como las causadas por *S. pneumoniae*, *N. meningitidis* y *H. influenzae*[2,3]. Otras IBI (por *E. coli* y *S. agalactiae*), más propias de niños más pequeños, no mostraron ese descenso[3]. Para nuestro conocimiento, estas variaciones no han sido analizadas en nuestro entorno ni tampoco se ha analizado si durante la pandemia varió la probabilidad de que un niño atendido en un SUP fuera diagnosticado de una IBI.

El objetivo principal de este estudio es analizar el impacto de la pandemia por el SARS-CoV-2 en la epidemiología de las IBI en SUP y en la probabilidad de que un niño menor de 14 años previamente sano que acude al SUP sea diagnosticado de una IBI.

En nuestro SUP existe un registro que incluye todas las IBI diagnosticadas desde 2008 ya explicado en previas publicaciones[4]. Se definió IBI como la identificación de una bacteria patógena en sangre o líquido cefalorraquídeo, excluyéndose los pacientes en los que se aisló una bacteria en el hemocultivo, clásicamente considerada como contaminante. Para este estudio, se analizó a los pacientes menores de 14 años previamente sanos diagnosticados de IBI en el SUP entre 2017 y 2022. Se compararon las características e incidencia de IBI en 2 periodos: prepandemia (2017-2019) y pandemia (marzo de 2020-diciembre de 2022). El periodo de pandemia se dividió en función de las medidas de protección adoptadas (higiénicas y de distancia social) y la afluencia a los SUP: 2020 (medidas más estrictas y menor afluencia al SUP) y 2021 y 2022 (medidas menos estrictas y mayor afluencia a los SUP). El estudio fue aprobado por el Comité de Ética e Investigación del hospital (código E22/36).

Durante el periodo de estudio se registraron en el SUP 269.105 episodios (153.736 prepandemia, con 4.270 episodios/mes, y 115.369 en pandemia, con 3.393 episodios/mes; $\Delta = -20{,}5\%$) y 119 pacientes menores de 14 años previamente sanos (0,04%) fueron diagnosticados de IBI. En el periodo prepandemia se diagnosticaron 70 IBI y se diagnosticaron 49 en la pandemia. Durante esta última, la probabilidad de diagnosticar de IBI a un paciente previamente sano varió de forma significativa: fue superior en 2020. En 2021, con medidas menos estrictas y mayor afluencia a los SUP, el número de IBI/mes fue inferior al de prepandemia, al igual que la probabilidad de diagnosticar de IBI a un paciente previamente sano. En 2022, de manera global, la situación fue similar a la prepandemia (tabla 1).

Durante la pandemia varió de manera notable la probabilidad de que un paciente previamente sano que consultaba en urgencias presentara una IBI. Cuando las medidas de protección fueron más estrictas y fue menor la afluencia a los SUP, la tasa de IBI/mes se mantuvo estable respecto a años previos. Sin embargo, esto comportó que la probabilidad de que un paciente previamente sano fuera diagnosticado de una IBI se incrementara de forma significativa, disminuyendo de nuevo cuando las medidas se relajaron y la afluencia a los SUP fue mayor. La disminución de la probabilidad de ser diagnosticado de una IBI cuando las medidas se relajaron era esperable por el aumento que se produce en la transmisión de infecciones virales, que pasan a ser mucho más frecuentes. Sin embargo, no encontramos explicación para esa disminución del número absoluto de pacientes diagnosticados de una IBI en el segundo año de la pandemia. Consideramos relevante que esta información sea conocida por los médicos que atienden a estos pacientes, ya que se podría pensar, incorrectamente, que, dado que existe una menor transmisibilidad de IBI por vía respiratoria, la probabilidad de que un niño que acude a Urgencias sea diagnosticado de IBI es menor. Además, la variación de la prevalencia de IBI podría también afectar al rendimiento de diferentes reglas de predicción clínica o de los sistemas utilizados para la identificación de pacientes con IBI. La no detección de bacterias transmisibles por vía respiratoria cuando las medidas de protección eran más estrictas, como la *N. meningitidis*, ya había sido reportada[2,3]. Por último, en el año 2022 se objetiva un importante repunte de las infecciones invasivas neumocócicas, que llegaron a ser el 40,9% de las IBI diagnosticadas.

A pesar de las limitaciones de nuestro estudio, derivadas de ser unicéntrico y de su pequeño tamaño muestral, pensamos que estos hallazgos refuerzan la necesidad de diseñar sistemas de vigilancia robustos que monitoricen la evolución de las IBI con el fin de poder utilizar estos datos para

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Tabla 1 Episodios totales e infecciones bacterianas invasivas (IBI) registradas en el servicio de urgencias pediátrico (SUP) antes y durante la pandemia por SARS-CoV-2

	Episodios en SUP	Episodios/mes	IBI	IBI/mes	IBI/episodios	Bacterias más prevalentes (%)
Prepandemia	153.736	4.270	70	1,94	1 IBI / 2.196	*S. pneumoniae* (18,6) *N. meningitidis* (18,6) *S. aureus* (17,1) *E. coli* (15,7) *S. agalactiae* (5,7)
Pandemia						
2020	21.746	2.175	19	1,90	1 IBI / 1.144*	*S. pneumoniae* (28,6) *S. aureus* (20,4) *N. meningitidis* (10)
2021	39.880	3.323	8	0,67*	1 IBI / 4.985*	*S. agalactiae* (10)
2022	53.743	4.478	22	1,83	1 IBI / 2.443	*E. coli* (10)

En el periodo de pandemia, los cambios destacables respecto a las bacterias responsables fueron la desaparición de *N. meningitidis* durante el 2021 y el aumento de *S. pneumoniae* en 2022 (9/22; 40,9% de las IBI diagnosticadas).
En menores de 3 meses, el *S. agalactiae* fue el principal causante de las IBI en la pandemia (33,3%) vs. *E. coli* (50%) en prepandemia.
* $p < 0,01$, al comparar con el periodo prepandemia.

que tanto el sistema sanitario como los profesionales estén preparados en caso de presentarse de nuevo una situación similar a la vivida durante la pandemia.

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Los autores no tienen conflictos de intereses.

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Validez de las ecuaciones CEEW para la estimación de peso en pacientes pediátricos españoles

Validity of CEEW equations for weight estimation in Spanish pediatric patients

Sra. Editora:

En ninguna otra población de pacientes hay más cálculo y manipulación de las dosis de medicamentos que en la edad pediátrica, por lo que la atención de emergencias pediátricas supone un verdadero reto para el personal sanitario. El conocimiento del peso exacto del niño es importante porque de este valor va a depender el cálculo de las dosis de medicamentos, pero no siempre es una información fácilmente disponible.

Para solventar este problema, tradicionalmente se han utilizado variedad de métodos de estimación de peso basados en variables indirectas, pero prácticamente todas presentan limitaciones de validez relacionadas con la diversidad étnica, biológica y sociodemográfica[1,2].

Una de las últimas estrategias de estimación de peso que se han publicado son las fórmulas Children's European Estimator of Weight (CEEW). La fórmula CEEW1 estima peso a

ARTÍCULOS RELACIONADOS CON CADA OBJETIVO

1. Caracterizar la presentación clínica de las IBI confirmadas en pacientes menores de catorce años.
    - Characteristics of children with microbiologically confirmed invasive bacterial infections in the emergency department. EJEM 2018.
    - Repeated Emergency Department Visits Among Children with Invasive Bacterial Infections. PIDJ 2021.
2. Describir la gravedad de las IBI en pacientes menores de catorce años.
    - Characteristics of children with microbiologically confirmed invasive bacterial infections in the emergency department. EJEM 2018.
    - Repeated Emergency Department Visits Among Children with Invasive Bacterial Infections. PIDJ 2021.
3. Analizar el valor de los test sanguíneos habituales (recuento leucocitario, número absoluto de neutrófilos, proteína C reactiva y procalcitonina) que se realizan para la identificación de IBI en pacientes menores de catorce años.
    - Markers for invasive bacterial infections in previously healthy children. Am J Emerg Med. 2021.
4. Evaluar la indicación de los test en sangre, en el manejo de niños de 3 a 24 meses de edad con fiebre sin focalidad y estabilidad clínica.
    - Prevalence of Occult Bacteremia in Infants With Very High Fever Without a Source. PIDJ 2018.

- Occult Bacteremia in Young Children with Very High Fever Without a Source: A Multicenter Study. PIDJ 2020.

5. Describir la presentación clínica de las infecciones invasivas por *E. Coli* y analizar posibles perfiles y su posible relación con la gravedad.
    - Paediatric *Escherichia coli* bacteraemia presentations and high-risk factors in the emergency department. Acta Paediatr 2021.
6. Describir la presentación clínica de la infección invasiva por estreptococo del grupo B y analizar su posible relación con su gravedad.
    - Late-onset Group B *Streptococcus* Bacteremia Evaluated in the Pediatric Emergency Department and Risk Factors for Severe Infection. PIDJ 2022.
7. Objetivo secundario: aunque no fuera objetivo de esta tesis, describir el impacto de una pandemia no esperada en la epidemiología de las IBI identificadas en un servicio de urgencias pediátrico.
    - Impact of the COVID-19 pandemic on pediatric invasive bacterial infections. An Pediatr (Engl Ed). 2023.

A pesar de no guardar una estrecha relación con los objetivos de la tesis, enumeramos otros artículos publicados en relación con las enfermedades infecciosas en urgencias de pediatría.

- van Houten CB, Naaktgeboren CA, Ashkenazi-Hoffnung L, Ashkenazi S, Avis W, Gangoiti I, Bont LJ et al; IMPRIND consortium. Expert panel diagnosis demonstrated high reproducibility as reference standard in infectious diseases. J Clin Epidemiol. 2019 Aug;112:20-27. doi: 10.1016/j.jclinepi.2019.03.010. Epub 2019 Mar 28. PMID: 30930247.
    - ISSN: 0895-4356
    - JCR: Science edition, 2019
    - Impact factor: 2,702
    - Quartil: Q1
    - Abstract:

      Objective: If a gold standard is lacking in a diagnostic test accuracy study, expert diagnosis is frequently used as reference standard. However, interobserver and intraobserver agreements are imperfect. The aim of this study was to quantify the reproducibility of a panel diagnosis for pediatric infectious diseases.

      Study design and setting: Pediatricians from six countries adjudicated a diagnosis (i.e., bacterial infection, viral infection, or indeterminate) for febrile children. Diagnosis was reached when the majority of panel members came to the same diagnosis, leaving others inconclusive. We evaluated intraobserver and intrapanel agreement with 6 weeks and 3

years' time intervals. We calculated the proportion of inconclusive diagnosis for a three-, five-, and seven-expert panel.

Results: For both time intervals (i.e., 6 weeks and 3 years), intrapanel agreement was higher (kappa 0.88, 95%CI: 0.81-0.94 and 0.80, 95%CI: NA) compared to intraobserver agreement (kappa 0.77, 95%CI: 0.71-0.83 and 0.65, 95%CI: 0.52-0.78). After expanding the three-expert panel to five or seven experts, the proportion of inconclusive diagnoses (11%) remained the same.

Conclusion: A panel consisting of three experts provides more reproducible diagnoses than an individual expert in children with lower respiratory tract infection or fever without source. Increasing the size of a panel beyond three experts has no major advantage for diagnosis reproducibility.

Keywords: Diagnosis; Expert panel; Gold standard; Infectious diseases; Reference standard; Reproducibility.

- Gangoiti I, Martinez-Fernandez E, Garmendia O, Diez A, Mintegi S. Impacto de la vacunación en embarazadas sobre la reemergencia de la tosferina y su forma de presentación en urgencias [Impact of whooping cough vaccine during pregnancy on the resurgence of the disease and its form of presentation in paediatric emergency departments]. An Pediatr (Engl Ed). 2020 Aug;93(2):129-131. Spanish. doi: 10.1016/j.anpedi.2019.11.002. Epub 2019 Dec 27. PMID: 31889662.
    - ISSN: 2341-2879

- JCR: Science edition, 2020
- Impact factor: 1,5
- Quartil: Q3
- Abstract:

  Introduction: The resurgence of pertussis led to immunize pregnant women in 2015. The objective is to analyse the impact of immunizing pregnant women on the resurgence and way of presentation of pertussis in a paediatric emergency department (ED).

  Methods: Retrospective cohort analysis between 2008 and 2017. We compared the episodes with a diagnosis of pertussis before and after immunizing pregnant women.

  Results: During the study period, 196 children were diagnosed with pertussis. In the pre-vaccine period, we diagnosed initially 1 episode of pertussis/8903 episodes in the ED vs 1/1178 in 2015, decreasing to 1/3203 episodes after vaccination. The median age of patients diagnosed with pertussis increased after vaccination (9 vs. 38 months, $p = 0,02$) and the admission rate dropped from 36.9% to 8.8% ($p < 0.01$).

  Conclusion: Vaccination has reversed the trend of rising pertussis cases in the paediatric ED, decreasing the number of more severe episodes.

- Funk AL, Florin TA, Kuppermann N, Tancredi DJ, Xie J, Gangoiti I, Freedman SB et al; Pediatric Emergency Research Network-COVID-19 Study Team. Outcomes of SARS-CoV-2-Positive Youths Tested in Emergency Departments: The Global PERN-COVID-19 Study. JAMA Netw Open. 2022 Jan

4;5(1):e2142322. Doi: 10.1001/jamanetworkopen.2021.42322. PMID: 35015063; PMCID: PMC8753506.

- ISSN: 2574-3805
- JCR: Science edition, 2022
- Impact factor: 4,108
- Quartil: Q1
- Abstract:

Importance: Severe outcomes among youths with SARS-CoV-2 infections are poorly characterized.

Objective: To estimate the proportion of children with severe outcomes within 14 days of testing positive for SARS-CoV-2 in an emergency department (ED).

Design, setting, and participants: This prospective cohort study with 14-day follow-up enrolled participants between March 2020 and June 2021. Participants were youths aged younger than 18 years who were tested for SARS-CoV-2 infection at one of 41 EDs across 10 countries including Argentina, Australia, Canada, Costa Rica, Italy, New Zealand, Paraguay, Singapore, Spain, and the United States. Statistical analysis was performed from September to October 2021.

Exposures: Acute SARS-CoV-2 infection was determined by nucleic acid (eg, polymerase chain reaction) testing.

Main outcomes and measures: Severe outcomes, a composite measure defined as intensive interventions during hospitalization (eg, inotropic support, positive pressure ventilation), diagnoses indicating severe organ impairment, or death.

Results: Among 3222 enrolled youths who tested positive for SARS-CoV-2 infection, 3221 (>99.9%) had index visit outcome data available, 2007 (62.3%) were from the United States, 1694 (52.6%) were male, and 484 (15.0%) had a self-reported chronic illness; the median (IQR) age was 3 (0-10) years. After 14 days of follow-up, 735 children (22.8% [95% CI, 21.4%-24.3%]) were hospitalized, 107 (3.3% [95% CI, 2.7%-4.0%]) had severe outcomes, and 4 children (0.12% [95% CI, 0.03%-0.32%]) died. Characteristics associated with severe outcomes included being aged 5 to 18 years (age 5 to <10 years vs <1 year: odds ratio [OR], 1.60 [95% CI, 1.09-2.34]; age 10 to <18 years vs <1 year: OR, 2.39 [95% CI 1.38-4.14]), having a self-reported chronic illness (OR, 2.34 [95% CI, 1.59-3.44]), prior episode of pneumonia (OR, 3.15 [95% CI, 1.83-5.42]), symptoms starting 4 to 7 days prior to seeking ED care (vs starting 0-3 days before seeking care: OR, 2.22 [95% CI, 1.29-3.82]), and country (eg, Canada vs US: OR, 0.11 [95% CI, 0.05-0.23]; Costa Rica vs US: OR, 1.76 [95% CI, 1.05-2.96]; Spain vs US: OR, 0.51 [95% CI, 0.27-0.98]). Among a subgroup of 2510 participants discharged home from the ED after initial testing and who had complete follow-up, 50 (2.0%; 95% CI, 1.5%-2.6%) were eventually hospitalized and 12 (0.5%; 95% CI, 0.3%-0.8%) had severe outcomes. Compared with hospitalized SARS-CoV-2-negative youths, the risk of severe outcomes was higher among hospitalized SARS-CoV-2-positive youths (risk difference, 3.9%; 95% CI, 1.1%-6.9%).

Conclusions and relevance: In this study, approximately 3% of SARS-CoV-2-positive youths tested in EDs experienced severe outcomes within 2 weeks of their ED visit. Among children discharged home from the ED,

the risk was much lower. Risk factors such as age, underlying chronic illness, and symptom duration may be useful to consider when making clinical care decisions.

- Funk AL, Kuppermann N, Florin TA, Tancredi DJ, Xie J, Gangoiti I, Freedman SB et al; Pediatric Emergency Research Network–COVID-19 Study Team. Post-COVID-19 Conditions Among Children 90 Days After SARS-CoV-2 Infection. JAMA Netw Open. 2022 Jul 1;5(7):e2223253. doi: 10.1001/jamanetworkopen.2022.23253. Erratum in: JAMA Netw Open. 2022 Aug 1;5(8):e2231131. PMID: 35867061; PMCID: PMC9308058.
    - ISSN: 2574-3805
    - JCR: Science edition, 2022
    - Impact factor: 4,108
    - Quartil: Q1
    - Abstract:

      Importance: Little is known about the risk factors for, and the risk of, developing post-COVID-19 conditions (PCCs) among children.

      Objectives: To estimate the proportion of SARS-CoV-2-positive children with PCCs 90 days after a positive test result, to compare this proportion with SARS-CoV-2-negative children, and to assess factors associated with PCCs.

      Design, setting, and participants: This prospective cohort study, conducted in 36 emergency departments (EDs) in 8 countries between March 7, 2020, and January 20, 2021, included 1884 SARS-CoV-2-positive children who completed 90-day follow-up; 1686 of these children were frequency

matched by hospitalization status, country, and recruitment date with 1701 SARS-CoV-2-negative controls.

Exposure: SARS-CoV-2 detected via nucleic acid testing.

Main outcomes and measures: Post-COVID-19 conditions, defined as any persistent, new, or recurrent health problems reported in the 90-day follow-up survey.

Results: Of 8642 enrolled children, 2368 (27.4%) were SARS-CoV-2 positive, among whom 2365 (99.9%) had index ED visit disposition data available; among the 1884 children (79.7%) who completed follow-up, the median age was 3 years (IQR, 0-10 years) and 994 (52.8%) were boys. A total of 110 SARS-CoV-2-positive children (5.8%; 95% CI, 4.8%-7.0%) reported PCCs, including 44 of 447 children (9.8%; 95% CI, 7.4%-13.0%) hospitalized during the acute illness and 66 of 1437 children (4.6%; 95% CI, 3.6%-5.8%) not hospitalized during the acute illness (difference, 5.3%; 95% CI, 2.5%-8.5%). Among SARS-CoV-2-positive children, the most common symptom was fatigue or weakness (21 [1.1%]). Characteristics associated with reporting at least 1 PCC at 90 days included being hospitalized 48 hours or more compared with no hospitalization (adjusted odds ratio [aOR], 2.67 [95% CI, 1.63-4.38]); having 4 or more symptoms reported at the index ED visit compared with 1 to 3 symptoms (4-6 symptoms: aOR, 2.35 [95% CI, 1.28-4.31]; ≥7 symptoms: aOR, 4.59 [95% CI, 2.50-8.44]); and being 14 years of age or older compared with younger than 1 year (aOR, 2.67 [95% CI, 1.43-4.99]). SARS-CoV-2-positive children were more likely to report PCCs at 90 days compared with those who tested negative, both among those who were not hospitalized (55 of

1295 [4.2%; 95% CI, 3.2%-5.5%] vs 35 of 1321 [2.7%; 95% CI, 1.9%-3.7%]; difference, 1.6% [95% CI, 0.2%-3.0%]) and those who were hospitalized (40 of 391 [10.2%; 95% CI, 7.4%-13.7%] vs 19 of 380 [5.0%; 95% CI, 3.0%-7.7%]; difference, 5.2% [95% CI, 1.5%-9.1%]). In addition, SARS-CoV-2 positivity was associated with reporting PCCs 90 days after the index ED visit (aOR, 1.63 [95% CI, 1.14-2.35]), specifically systemic health problems (eg, fatigue, weakness, fever; aOR, 2.44 [95% CI, 1.19-5.00]).

Conclusions and relevance: In this cohort study, SARS-CoV-2 infection was associated with reporting PCCs at 90 days in children. Guidance and follow-up are particularly necessary for hospitalized children who have numerous acute symptoms and are older.

MÉTODO DE DESARROLLO DE ARTÍCULOS

Trabajos basados en un registro prospectivo unicéntrico

- Gangoiti I, Valle JR, Sota M, Martinez-Indart L, Benito J, Mintegi S. Characteristics of children with microbiologically confirmed invasive bacterial infections in the emergency department. Eur J Emerg Med. 2018 Aug;25(4):274-280. doi: 10.1097/MEJ.0000000000000453. PMID: 28118320.
- Gangoiti I, Fernandez CL, Gallego M, Gomez B, Benito J, Mintegi S. Markers for invasive bacterial infections in previously healthy children. Am J Emerg Med. 2021 Oct;48:83-86. doi: 10.1016/j.ajem.2021.04.018. Epub 2021 Apr 13. Erratum in: Am J Emerg Med. 2021 Apr 22: PMID: 33862390.
- Gangoiti I, Gorostizaga Z, Aranzamendi M, Gomez B, Benito J, Mintegi S. Repeated Emergency Department Visits Among Children with Invasive Bacterial Infections. Pediatr Infect Dis J. 2021 May 1;40(5): e205-e207. doi: 10.1097/INF.0000000000003062. PMID: 33464016
- Martin-Irazabal G, Gangoiti I, Gomez B, Lizarraga L, Mintegi S. Impact of the COVID-19 pandemic on pediatric invasive bacterial infections. An Pediatr (Engl Ed). 2023 Mar;98(3):228-229. doi: 10.1016/j.anpede.2023.01.013. Epub 2023 Feb 20. PMID: 36813615; PMCID: PMC9940794

Estos trabajos son el resultado de un estudio de cohorte basado en un registro prospectivo iniciado en 2008. La base de datos ha recopilado las IBI que se han diagnosticado en pacientes menores de 14 años en un servicio de urgencias pediátrico de un hospital terciario. Este servicio de urgencias forma parte de un hospital docente terciario y atiende cada año a 55.000 pacientes menores de 14 años.

Cada paciente diagnosticado de un IBI en el servicio pediátrico de urgencias se identifica a través de los registros electrónicos propios del hospital. Mensualmente, el investigador principal recibe un informe con los cultivos de todas las muestras que supervisa el servicio de microbiología. También registra la identificación de *N. meningitidis y S. pneumoniae* por detección a partir de técnicas basadas en la PCR que se han realizado en muestras de sangre y LCR. Todo ello se revisa a posteriori en el informe del episodio adherido a los Servicios de Urgencias Pediátricas del Sistema Público de Salud.

En el registro se recogieron los siguientes datos:

- Edad
- Sexo
- Antecedentes
- Año y mes en que se ha realizado la consulta
- Estado de vacunación frente al neumococo
- Temperatura máxima registrada en el hogar
- Temperatura registrada en el servicio pediátrico de urgencias
- Consulta previa y posterior relacionada con el mismo episodio (partiendo de la fecha en la que se ha obtenido la cultura sanguínea)
- Posibles síntomas asociados
- Situación al llegar al servicio de urgencias (triángulo de evaluación pediátrica)
- Exploración física
- Test de sangre (recuento de leucocitos, recuento absoluto de neutrófilos, proteína C reactiva, procalcitonina)
- Pruebas de identificación por reacción en cadena de la polimerasa y hemocultivo
- Radiografía torácica

- Pruebas en orina y líquido cefalorraquídeo, análisis bioquímico, pruebas de identificación por reacción en cadena de la polimerasa y cultivos
- Otros cultivos
- Microorganismo aislado
- Diagnóstico final
- Destino
- Evolución

Las definiciones más importantes han sido las que hemos ido citando en la introducción de esta tesis y que se han ido repitiendo artículo por artículo.

- Infección bacteriana invasiva (IBI): Identificación de una verdadera bacteria patógena en sangre y/o líquido cefalorraquídeo por cultivo bacteriano y/o detección genómica de *N. meningitidis* y *S. pneumoniae* mediante la técnica PCR (En nuestro caso, RealCycler MENE y RealCycler MENELI; Progenie Molecular, Valencia, España). La especie aislada clásicamente definida como contaminante (incluyendo *Staphylococcus epidermidis*, *Propionibacterium acnes, Streptococcus viridans, Corynebacterium* spp., otros difteroides y otros) en un paciente previamente sano será rechazada. Para el diagnóstico definitivo de la infección asociada al catéter eran necesarios resultados positivos de los extremos distales de los catéteres o del cultivo sanguíneo extraído de los catéteres/dispositivos.
- Paciente previamente sano: Paciente que no padece ninguno de los siguientes factores de riesgo que pueden facilitar una infección grave: inmunodepresión (enfermedad oncológica, insuficiencia renal crónica, paciente trasplantado, paciente que sufre anemia drepanocítica, paciente que toma medicación que causa

inmunosupresión, recién nacido muy prematuro,...); presencia de un dispositivo mecánico (catéter permanente, válvula de derivación ventriculoperitoneal); o paciente que ha sufrido un procedimiento diagnóstico-terapéutico invasivo en los 10 días previos.

- Paciente con buen aspecto: pacientes con un triángulo de evaluación pediátrico estable (Gausche-Hill M, 2003) cuando llegan al servicio de urgencias pediátrico.
- Bacteriemia oculta: Aislamiento de una bacteria real en la sangre del paciente que, además de la fiebre, no presenta ningún otro signo ni síntoma.
- Sepsis: es el síndrome de respuesta inflamatoria sistémica del organismo ante una posible infección y/o infección confirmada (Goldstein B, 2005).
- Sepsis severa: a la definición de sepsis acordada por Goldstein et al. se han añadido los siguientes criterios: disfunción cardiovascular, síndrome de dificultad respiratoria aguda y/o disfunción de otros dos sistemas (Goldstein B, 2005) (Gómez Cortés, 2020).
- Shock séptico: Shock séptico, sepsis y disfunción orgánica no estabilizada por la administración de líquidos isotónicos de hasta 40ml/kg (Goldstein B, 2005).
- Criterios de gravedad: mantenimiento de secuelas permanentes o de muerte en el plazo de 12 meses como consecuencia de sufrir el IBI. Se definirá secuela como estado de morbilidad que ha aparecido como consecuencia de la IBI. Incluso la necesidad del ingreso en unidades de cuidados intensivos se ha definido como criterio de gravedad.

Definiciones específicas:

- Valores analíticos normales: De acuerdo con los valores generalmente más aceptados, se consideraron valores normales: recuento leucocitario entre 5.000 y

15.000/mm^3; número absoluto de neutrófilos entre 1.500 y 10.000/mm^3; Proteína C reactiva por debajo de 20 mg/L y procalcitonina por debajo de 0,5 ng/ml.

- Fiebre sin foco: Se denomina fiebre que no presenta signos o síntomas que puedan indicar su origen, tales como tos, diarrea, inflamación de amígdalas, auscultación patológica, polipnea, signos meníngeos, ...

En cuanto al análisis estadístico se realizó con el programa SPSS Statistics for Windows, utilizando la versión 21.0 y 23.0 (IBM, Armonk, Nueva York, EEUU). Las variables cualitativas se describieron utilizando frecuencias y porcentajes absolutos y las variables continuas utilizando medias y desviaciones estándar o medianas y rangos intercuartiles. Para el análisis de la relación entre variables cualitativas se utilizó la prueba Chi-cuadrado. Los patrones de regresión de Poisson se utilizaron para analizar las tasas de incidencia de IBI neumococo en determinados periodos de tiempo. Se realizó una regresión logística binaria multivariante con el fin de identificar factores de riesgo independientes relacionados con la mayor gravedad del proceso. Inicialmente se realizó un análisis de regresión logística de una sola variable. Todas las variables con valor P inferior a 0,2 se incluyeron en un modelo multivariante no automático y posteriormente el valor P inferior a 0,05 para su inclusión en el último modelo multivariante. Los resultados del modelo se presentaron como odds ratios e intervalos de confianza del 95%. También se calculó la curva de especificidad y rendimiento diagnóstico (curva ROC) y la superficie bajo la curva. La capacidad de adaptación del modelo fue evaluada mediante la prueba Hosmer-Lemeshow.

Salvo en el estudio de caracterización de pacientes, en los tres restantes sólo se incluyeron los modelos de los pacientes previamente sanos. En el artículo que tenía como objetivo investigar los biomarcadores en sangre, se calculó la sensibilidad de cada uno en función del diagnóstico final y microorganismo causante. Por otro lado, en el artículo cuyo

propósito era conocer el impacto de la pandemia, se diferenciaron dos periodos con el objetivo de analizar la incidencia y características de las IBI, la época pre-pandemia (2017-2019) y la época pandémica entre marzo de 2020 y diciembre de 2022.

Trabajo basado en una investigación unicéntrica

- Gangoiti I, Rodriguez E, Zubizarreta A, Benito J, Mintegi S. Prevalence of Occult Bacteremia in Infants With Very High Fever Without a Source. Pediatr Infect Dis J. 2018 Nov;37(11): e271-e273. doi: 10.1097/INF.0000000000001955. PMID: 29462106.

Estudio retrospectivo, descriptivo y analítico realizado en el Servicio de Urgencias Pediátricas de un hospital docente terciario que forma parte del Sistema Público de Salud. La población investigada fueron los lactantes de 3 a 24 meses atendidos en el servicio pediátrico de urgencias desde enero de 2013 hasta diciembre de 2016. Para ello se definieron una serie de criterios de inclusión:

- Paciente de 3 a 24 meses con una temperatura objetivada en el domicilio o en el hospital igual o superior a 40,5 ºC y previamente sano.
- Paciente con buen aspecto basado en el triángulo de evaluación pediátrica.
- Paciente con hemocultivo extraído.

La variable resultado fue la identificación de una bacteria patógena real, bien por el crecimiento en sangre o por una detección positiva basada en la PCR para meningococo/neumococo.

Se recogieron los siguientes datos:

- Edad
- Sexo
- Antecedentes
- Año y mes de la consulta
- Estado de vacunación frente al neumococo
- Temperatura máxima registrada en el hogar

- Temperatura registrada en los servicios pediátricos de urgencia
- Consulta previa y posterior relacionada con el mismo episodio (partiendo de la fecha en la que se ha obtenido el cultivo de sangre.
- Posibles síntomas asociados
- Situación al llegar al servicio pediátrico de urgencias
- Exploración física
- Pruebas de sangre (recuento de leucocitos, recuento absoluto de neutrófilos, proteína C reactiva, procalcitonina)
- Pruebas de identificación por PCR y hemocultivo
- Radiografía torácica
- Análisis bioquímico y cultivo en orina y líquido cefalorraquídeo y pruebas de identificación por PCR en líquido cefalorraquídeo.
- Otras pruebas microbiológicas
- Microorganismo aislado
- Diagnóstico final
- Destino
- Evolución

Las definiciones son las mismas que se han explicado anteriormente.

Durante el tiempo de estudio, a los niños entre 3 y 24 meses de edad que fueron atendidos en el servicio de urgencias que consultaron con fiebre sin foco de 40,5 ºC o más, independientemente de su estado vacunal, la recomendación era realizar las siguientes pruebas complementarias hemocultivo, recuento leucocitario, número absoluto de neutrófilos, proteína C reactiva, procalcitonina, tira reactiva de orina y prueba PCR para neumococo y meningococo en sangre. Otras pruebas (urocultivo, radiografía, ...) se realizaron según la decisión del médico que atendió al paciente.

En cuanto al análisis estadístico, este se realizó utilizando la versión 23.0 del programa SPSS Statistics for Windows (IBM, Armonk, Nueva York, EE). Las variables cualitativas se describieron utilizando frecuencias y porcentajes absolutos y las variables continuas utilizando la media, la desviación estándar o mediana y rango intercuartil. Para el análisis de la relación entre variables cualitativas se utilizó la prueba Chi-cuadrado.

Trabajos basados en investigaciones multicéntricas (realizadas en el seno del grupo de trabajo de enfermedades infecciosas de SEUP)

Estudio observacional prospectivo multicéntrico

- Gangoiti I, Zubizarreta A, Elgoibar B, Mintegi S; Infectious Diseases Working Group, Spanish Society of Pediatric Emergencies (SEUP). Occult Bacteremia in Young Children with Very High Fever Without a Source: A Multicenter Study. Pediatr Infect Dis J. 2020 Dec;39(12):e462-e464. doi: 10.1097/INF.0000000000002891. PMID: 32898089

Se trata de una investigación prospectiva multicéntrica. En nombre del Grupo de Trabajo de Enfermedades Infecciosas de la Sociedad Española de Medicina de Urgencias de Pediatría, aprobado por la Red de Investigación de la Sociedad Española de Urgencias Pediátricas, se llevó a cabo un estudio observacional prospectivo multicéntrico basado en una cohorte de lactantes febriles sin foco previamente sanos con una temperatura igual o superior a 40,5 ºC atendidos en 6 servicios de urgencias pediátricas en España. Los pacientes fueron reclutados prospectivamente desde el 1 de enero de 2018 hasta el 31 de diciembre de 2019.

Los criterios de inclusión, los manejos terapéuticos, las definiciones y la variable resultado que se plantearon son las mismas que en la investigación unicéntrica comentada previamente.

Todos los datos de los pacientes reclutados fueron introducidos por los médicos encargados de sus cuidados, en un cuestionario electrónico específico a través de Google Drive®. Una vez iniciada la investigación, se procedió a la entrega de los cuestionarios a los responsables de todos los servicios de urgencias participantes, con el fin de garantizar la claridad del método, resolver dudas y, en consecuencia, mejorar la calidad de los datos

recabados. El cuestionario fue cumplimentado por el médico que firmaba el alta domiciliaria o el alta de hospitalización desde el servicio de urgencias, con el fin de obtener información completa sobre las características y resultados del paciente y también del servicio de urgencias pediátrico. Los cuestionarios ya cumplimentados sólo estaban disponibles para el investigador principal.

En cuanto al análisis estadístico, se realizó utilizando la versión 23.0 del programa SPSS Statistics for Windows (IBM, Armonk, Nueva York, EEUU). Las variables categóricas se describen por frecuencias y porcentajes absolutos y las variables continuas por media y desviación estándar o mediana y rango intercuartil. Se utilizó la prueba Chi-cuadrado para analizar la relación entre variables categóricas. Inicialmente, el objetivo de la muestra total de la investigación se fijó en 500 pacientes. Sin embargo, después de que la cifra alcanzara los 200 pacientes y los resultados parecieran tan significativos, el investigador principal se puso en contacto con la revista en la que se publicó el estudio unicéntrico y se acordó si continuar o no con el reclutamiento (se estimaron al menos dos años más para alcanzar el objetivo marcado). Por la importancia que podían tener los resultados, nos solicitaron que se suspendiera el reclutamiento y se hiciera un intento de publicarlo.

Artículos que son el resultado de análisis secundarios a partir de un gran registro prospectivo

- Elgoibar B, Gangoiti I, Garcia-Garcia JJ, Hernandez-Bou S, Gomez B, Martinez Indart L, Mintegi S; Bacteremia Study Working Group from the Infectious Diseases Working Group, Spanish Society of Pediatric Emergencies (SEUP). Paediatric *Escherichia coli* bacteraemia presentations and high-risk factors in the emergency department. Acta Paediatr. 2021 Mar;110(3):1032-1037. doi: 10.1111/apa.15549. Epub 2020 Sep 9. PMID: 32815584

- Ecclesia FG, Alonso Cadenas JA, Gómez B, Gangoiti I, Hernández-Bou S, de la Torre Espí M; Bacteremia Study Working Group from the Infectious Diseases Working Group, Spanish Society of Pediatric Emergencies. Late-onset Group B *Streptococcus* Bacteremia Evaluated in the Pediatric Emergency Department and Risk Factors for Severe Infection. Pediatr Infect Dis J. 2022 Jun 1;41(6):455-459. doi: 10.1097/INF.0000000000003520. Epub 2022 May 6. PMID: 35446825.

Estos artículos son el resultado de un registro prospectivo llevado a cabo en 23 servicios de urgencias en España, fruto de los análisis secundarios de un gran registro prospectivo que tenía como objetivo caracterizar las bacteriemias que se detectan en la edad pediátrica. En 2010, la Sociedad Española de Medicina de Urgencias de Pediatría, liderada por el Grupo de Trabajo de Enfermedades Infecciosas, propuso establecer un registro multicéntrico prospectivo de los hemocultivos positivos aislados en los servicios de urgencias de pediatría en España. El reclutamiento prospectivo de pacientes con edades comprendidas entre los niños recién nacidos y los 20 años se produjo entre 2011 y 2016.

Durante 2011 participaron en el reclutamiento 15 servicios de urgencias pediátricas, 22 durante 2012, 21 durante 2013, 19 durante 2014, 17 durante 2015 y 2016.

Para alcanzar el objetivo de estos estudios se analizaron los pacientes en los que en su muestra de sangre se aislaron el estreptococo del grupo B y *E. Coli*.

Las definiciones más importantes fueron las mismas que se establecieron en el resto de investigaciones. Se definió el buen aspecto del paciente a partir de la valoración del triángulo de evaluación pediátrica. En los antecedentes personales se tuvieron en cuenta factores que aumentan el riesgo de bacteriemia (inmunosupresión, enfermedad oncológica, presencia de dispositivos y otros). Para el diagnóstico de la sepsis se tuvieron en cuenta los criterios publicados por Goldstein et al; el paciente que cumplió con el concepto de sepsis grave fue declarado de esta forma y se mantuvo la definición de bacteriemia oculta. Para el artículo cuyo objetivo era investigar el estreptococo del grupo B, la bacteriemia tardía producida por este microorganismo se definió como la infección producida en los pacientes entre 7 y 89 días. Como factores de riesgo de la infección por estreptococo del grupo B se estableció la colonización o el desconocimiento del estado de colonización materna y el parto ocurrido antes de las 37 semanas.

Los criterios que definieron la gravedad (tuvieron que cumplir al menos uno) fueron: muerte, secuelas, estancia en Unidad de Cuidados Intensivos (UCI) y aparición de complicaciones agudas graves (insuficiencia renal o hepática, síndrome de insuficiencia respiratoria aguda, ictus, aparición de convulsiones graves, ...).

Para identificar los tipos de presentaciones de bacteriemia por *E. coli* se utilizaron análisis de correspondencia múltiple y el análisis Clúster. Para el análisis de correspondencia múltiple utilizamos las siguientes variables categóricas: sexo, edad, aspecto basado en el triángulo de evaluación pediátrico, estado previamente sano o no, fiebre, resto de

síntomas, exploración física. Se formaron subgrupos con algunas variables. En el caso de la edad, se crearon grupos de pacientes menores de 3 meses, de 3 a 12 meses y mayores de 12 meses. Basándose en el triángulo de evaluación, se clasificaron según si la apariencia era normal o no, la parte circulatoria era normal o no y la parte respiratoria era normal o no. Posteriormente se realizó el análisis Clúster. Para ello, el conjunto de datos que a priori son heterogéneos entre sí debe convertirse en grupos homogéneos. Los factores obtenidos en los análisis de correspondencia múltiple fueron utilizados como variables para realizar el análisis Clúster y obtener una adecuada agrupación de las diferentes presentaciones de bacteriemia por *E. coli*. Para crear los Clústeres se utilizó la distancia cuadrada euclidiana y el método Ward. Este método combinó el análisis de correspondencia con el análisis de Clúster para clasificar los casos de bacteriemia por *E. coli* en grupos. En resumen, esta técnica matemática divide a la población en diferentes grupos no especificados previamente; los pacientes de cada grupo distribuido son similares entre sí, pero diferentes a los de los otros grupos. Finalmente, se utilizó el test Chi-cuadrado para analizar la relación entre la gravedad y los diferentes tipos de presentaciones de bacteriemia *E. coli.*

En el estudio que se realizó en el caso del estreptococo del grupo B, las variables con distribución normal se describen como medias y desviaciones estándar y las que no tenían una distribución normal como intervalos entre mediana y cuartil. Para los datos normalmente distribuidos, se utilizaron pruebas T de dos colas para comparar los valores medios entre los grupos y Mann-Whitney U para el resto de datos. Las variables categóricas se expresaron en porcentajes y se compararon utilizando la prueba Chi-cuadrado. Para identificar la bacteriemia causada por estreptococo del grupo B se calculó la sensibilidad de cada uno de los biomarcadores que se analizaban en sangre y la sensibilidad para diferenciar la enfermedad grave/no grave. Se realizó una regresión

logística binaria multivariante con el fin de identificar factores de riesgo independientes relacionados con la mayor gravedad del proceso. En el análisis de una sola variable, como prueba adicional, se realizó una regresión con eliminación retroactiva para estas variables binarias con valor $p < 0,2$. Los análisis estadísticos se realizaron en este caso utilizando el STATA v.15

ÉTICA

Todos los trabajos realizados cuentan con la aprobación del Comité de Ética, ya sea hospitalario o vasco. Códigos:

• La apertura del registro unicéntrico fue autorizada por el Comité Ético de Investigación Clínica del Hospital, con código de informe E11/52. Durante la pandemia se realizó una nueva solicitud de autorización y el código del informe autorizado es el siguiente: E22/36.

• El trabajo unicéntrico y multicéntrico que ha investigado a lactantes con fiebre muy elevada para deducir la prevalencia de bacteriemia, fue autorizado por el Comité Ético de Investigación Clínica del País Vasco y los códigos internos fueron E16/11 y PI2017169, respectivamente.

• Los trabajos derivados del gran estudio multicéntrico fueron autorizados por el Comité Ético de Investigación Clínica del País Vasco con el código interno PI2011040.

RESULTADOS

PUBLICACIONES POR OBJETIVOS

Caracterizar la presentación clínica de las IBI confirmadas y describir la gravedad de las IBI en pacientes menores de catorce años

- Gangoiti I, Valle JR, Sota M, Martinez-Indart L, Benito J, Mintegi S. Characteristics of children with microbiologically confirmed invasive bacterial infections in the emergency department. Eur J Emerg Med. 2018 Aug;25(4):274-280. doi: 10.1097/MEJ.0000000000000453. PMID: 28118320.

A lo largo de los ocho años que duró el periodo de estudio se registraron en el SUP 456.830 consultas correspondientes a pacientes menores de 14 años. De ellos, en 223 se diagnosticó una IBI (0,048%, IC 95%: 0,047-0,049), 187 (83,9%) eran previamente sanos.

Fueron 126 (56,5%) los varones y la edad media fue de 19 meses (intervalo intercuartil: de 5 meses a 2 años) *(características, ver Table 1)*. Casi la mitad [102 (45,7%)] se diagnosticaron entre octubre y enero. *S. pneumoniae* [68 (30,5%)] y *N. meningitidis* [42 (18,8%)], representaron casi el 50% de los casos (*ver Table 2*). Se observó una tendencia descendente de la IBI neumocócica en el periodo 2008-2015, si bien este efecto no es estadísticamente significativo *(ver Figure 1)*. *S. pneumoniae* se serotipó en 57 pacientes, 37 de los cuales (64,9%) estaban incluidos en la vacuna neumocócica 13valente.

El diagnóstico final de los pacientes, la edad y las características clínicas del paciente variaron sustancialmente en función de la bacteria aislada *(ver Table 3)*.

En total, 147 pacientes (65,9%) fueron hospitalizados (64 en la UCI, el 28,7% del total). La evolución de la amplia mayoría [211 (94,6%)] fue favorable, aunque en cuatro casos (1,8%) el paciente falleció y otros 8 (3,6%) sufrieron secuelas persistentes. En otros 3 pacientes el dispositivo de derivación ventriculoperitoneal fracasó y fue necesaria la sustitución.

Se definieron factores de riesgo independientes para una mayor gravedad, el haber sido atendido en los servicios de urgencias durante las primeras 24 horas de la enfermedad, la presencia de algún otro síntoma además de fiebre y la ausencia de un triángulo de evaluación pediátrica estable al llegar al servicio de urgencias. La superficie por debajo de la curva de especificidad y rendimiento diagnóstico (ROC) fue de 0,805 (IC 95%: 0,741-0,868) y el valor p para la prueba Hosmer-Lemeshow fue de 0,356.

Las IBI más graves fueron las infecciones meningocócicas (odds ratio 12,3, IC 95%: 5,3-28,4), así como la sepsis o meningitis frente a otros diagnósticos (82,1%, 44% y 7%, respectivamente, $P < 0,001$). La IBI se diagnosticó en una segunda visita a urgencias en 32 pacientes (14,3%), 13 *S. pneumoniae* y 7 *N. meningitidis*. De ellos, seis fueron diagnosticados finalmente de sepsis y uno de ellos falleció. De los 32 pacientes diagnosticados de IBI en la segunda consulta, cuatro (12,5%) fallecieron o sufrieron secuelas permanentes [vs. en ocho de los 191 diagnosticados en la primera visita (4,1%), $p = 0,07$].

Table 1: Characteristics of the patients diagnosed with an invasive bacterial infection.

	n **(%)**	**95% CI**
Sex (male)	126 (56.5)	50–63
Age: < 12 months	86 (38.6)	32.2–45
Increased risk of invasive bacterial infection		
No	187 (83.8)	78.9–88.6
Immunological and/or with central venous catheter	21 (9.5)	5.6–13.3
Others	15 (6.7)	3.4–9.9
Pneumococcal vaccine dose received		
Unknown	24 (10.8)	6.7–14.8
None	117 (52.5)	45.9–59
1 doses	9 (4)	1.4–6.5
2 doses	13 (5.8)	2.7–8.8
3 doses	29 (13)	8.5–17.4
4 doses	31 (13.9)	9.3–18.4
Duration of fever		
Afebrile	8 (3.6)	1.1–6
< 6 h	64 (28.7)	22.7–34.6
6–24 h	63 (28.3)	22.3–34.2
> 24 h	88 (39.4)	33–45.8
Symptoms		
Fever only	64 (28.7)	22.7–34.6
Respiratory	44 (19.7)	14.5–24.9
Digestive	60 (26.9)	21.1–32.7
Neurological	35 (15.7)	10.9–20.5
Rash	21 (9.4)	5.5–13.2
Osteoarticular and/or soft tissue	19 (8.5)	4.8–12.1
Others	14 (6.3)	3.1–9.5
Well appearing upon arrival at the ED	165 (74)	68.2–79.7
Physical examination		
Normal	92 (41.3)	34.8–47.7
Rash	52 (23.3)	17.7–28.8
Abnormal pulmonary auscultation	28 (12.6)	8.2–16.9
Alteration of the central nervous system	32 (14.3)	9.7–18.9
Osteoarticular and/or soft tissue findings	15 (6.7)	3.4–9.9
Others	18 (8.1)	4.5–11.6

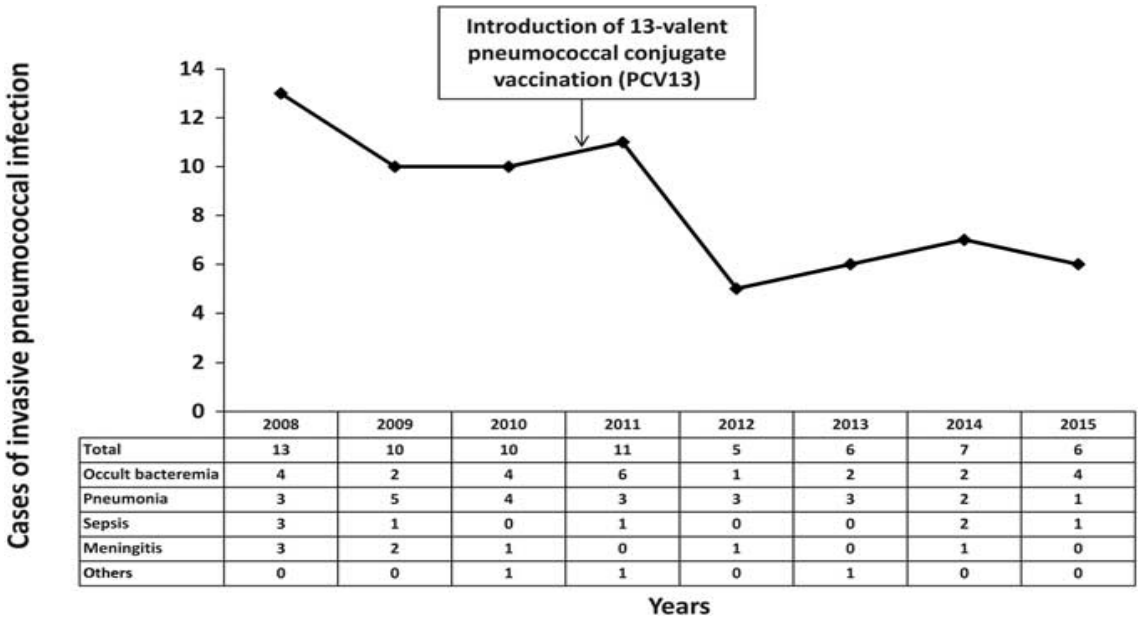
***ED**, emergency department; **CI**, confidence interval.*

Table 2. Bacteria isolated from patients with an invasive bacterial infection.

Bacteria	*n* (%)	95% CI
Streptococcus pneumoniae	68 (30.5)	24.5–36.5
Neisseria meningitidis	42 (18.8)	13.7–23.9
Escherichia coli	33 (14.8)	10.1–19.5
Staphylococcus aureus	25 (11.2)	7.1–15.3
Streptococcus agalactiae	9 (4)	1.4–6.6
Streptococcus pyogenes	9 (4)	1.4–6.6
***Staphylococcus coagulase* (−)**	8 (3.6)	1.1–6.1
Enterococcus faecalis	6 (2.7)	0.6–4.8
Others	23 (10.3)	6.4–14.4

Data are expressed as n (%) and 95% CI; ***CI****, confidence interval.*
Others: Salmonella spp. 5, Pseudomonas aeruginosa 3, Klebsiella spp. 3, Proteus mirabillis 2, Haemophilus influenzae 2, Listeria monocytogenes 1, Moraxella catharralis 1, Morganella morgagni 1, Propionebacterium acnes 1; Streptococcus mitis 1, Staphylococcus lugdunensis 1, Streptococcus salivarius 1; Campylobacter jejuni 1.

Figure 1. Cases of invasive pneumococcal bacterial infection by year.



	2008	2009	2010	2011	2012	2013	2014	2015
Total	13	10	10	11	5	6	7	6
Occult bacteremia	4	2	4	6	1	2	2	4
Pneumonia	3	5	4	3	3	3	2	1
Sepsis	3	1	0	1	0	0	2	1
Meningitis	3	2	1	0	1	0	1	0
Others	0	0	1	1	0	1	0	0

Table 3. Isolated bacteria related to the final diagnosis of the patients.

	Occult bacteraemia	Sepsis/ shock	Pneumonia	Urinary tract infection	Meningitis	Arthritis/ osteomyelitis	Cellulitis/ abscess	Others	Total
Streptococcus Pneumoniae	25 (36.8)	8 (11.8)	24 (35.3)	0	8 (11.8)	0	0	3 (4.3)	68 (30.5)
	25.3–48.26	4.1–19.5	23.9–46.7		4.1–19.5			0–9.3	24.5–36.5
Neisseria meningitidis	2 (4.8)	30 (71.4)	0	0	10 (23.8)	0	0	0	42 (18.9)
	0–11.26	57.7–85.1			10.9–36.7				13.7–23.9
Escherichia coli	2 (6.1)	3 (9.1)	0	26 (78.8)	2 (6.1)	0	0	0	33 (14.8)
	0–14.2	0–18.9		64.8–92.8	0–14.27				10.1–19.5
Staphylococcus aureus	8 (32.0)	1 (4.0)	1 (4.0)	1 (4.0)	0	13 (52.0)	0	1 (4.0)	25 (11.2)
	13.7–50.3	0–11.7	0–11.7	0–11.7		32.4–71.6		0–11.7	7.1–15.3
Streptococcus agalactiae	2 (22.2)	6 (66.7)	0	0	1 (11.1)	0	0	0	9 (4)
	0–49.4	35.9–97.5			0–31.6				1.4–6.6
Streptococcus pyogenes	3 (33.3)	2 (22.2)	1 (11.1)	0	0	0	3 (33.3)	0	9 (4)
	2.5–64.1	0–49.4	0–31.6				2.5–64.1		1.4–6.6
Staphylococcus coagulase (−)	5 (62.5)	1 (12.5)	0	0	1 (12.5)	0	1 (12.5)	0	8 (3.6)
	28.9–96.0	0–35.4			0–35.4		0–35.4		1.1–6.1
Enterococcus faecalis	4 (66.7)	0	1 (16.7)	0	1 (16.7)	0	0	0	6 (2.7)
	29–100		0–46.5		0–46.5				0.6–4.8
Others	9 (39.1)	5 (21.7)	0	0	2 (8.7)	0	1 (4.3)	6 (26.1)	23 (10.3)
	19.2–59	4.8–38.5			0–20.2		0–12.6	8.1–44.1	6.3–14.3
Total	60 (26.9)	56 (25.1)	27 (12.1)	27 (12.1)	25 (11.2)	13 (5.8)	5 (2.2)	10 (4.5)	223
	21.1–32.7	19.4–30.8	7.8–16.4	7.8–16.4	7.1–15.3	2.7–8.9	0.3–4.1	1.8–7.2	

Table 4: Clinical characteristics of the invasive infections caused by the most common bacteria.

	Streptococcus pneumoniae (*n* = 68)[a]	*Neisseria meningitidis* (*n* = 42)[b]	*Escherichia coli* (*n* = 33)	*Staphylococcus aureus* (*n* = 25)[c]	*Streptococcus pyogenes* (*n* = 9)	*Streptococcus agalactiae* (*n* = 9)
Age (months) [median (interquartile range)] (25–75%)	19 (11.2–35)	20 (7.7–48)	1 (0–9)	84 (18–126)	39 (20–72)	0 (0–1.5)
Previously healthy	66 (97.1)	42 (100)	28 (84.8)	20 (80)	9 (100)	7 (77.8)
Duration of fever < 12 h	21 (30.9)	17 (40.5)	20 (60.6)	7 (28)	3 (33.3)	9 (100)
Fever > 39°C	53 (77.9)	28 (66.7)	12 (36.4)	13 (52)	7 (77.8)	2 (22.2)
Associated symptoms						
None	16 (23.5)	8 (19)	18 (54.5)	7 (28)	0	4 (44.4)
Respiratory	30 (44.1)	4 (9.5)	7 (21.2)	0	0	0
Rash	0	17 (40.5)	0	0	3 (33.3)	0
Neurological	13 (19.1)	13 (31)	1 (3)	1 (4)	1 (11.1)	1 (11.1)
Stable on arrival	42 (61.8)	24 (57.1)	31 (93.9)	24 (96)	7 (77.8)	6 (66.7)
Physical examination						
None	25 (36.8)	8 (19)	27 (81.8)	7 (28)	1 (11.1)	4 (44.4)
Abnormal PA	21 (30.9)	0	0	1 (4)	0	0
Rash	8 (11.8)	32 (76.2)	1 (3)	2 (8)	5 (55.6)	0
CNS alteration	14 (20.6)	2 (4.8)	3 (9.1)	0	0	4 (44.4)
Final diagnosis						
Occult bacteraemia	25 (36.8)	2 (4.8)	2 (6.1)	8 (32)	3 (33.3)	2 (22.2)
Sepsis	8 (11.8)	30 (71.4)	3 (9.1)	1 (4)	2 (22.2)	6 (66.7)
Pneumonia	24 (35.3)	0	0	1 (4)	1 (11.1)	0
Urinary infection	0	0	26 (78.8)	1 (4)	0	0
Meningitis	8 (11.8)	10 (23.8)	2 (6.1)	0	0	1 (11.1)
OAI	0	0	0	13 (52)	3 (33.3)	0
Others	3 (4.4)	0	0	1 (4)	0	0
Evolution						
Death	2 (2.9)	0	0	0	1 (11.1)	0
Sequelae	5 (7.4)	3 (7.1)	0	0	0	0

***CNS**, central nervous system; **OAI**, osteoarticular and/or soft tissue infection; **PA**, pulmonary auscultation.*
[a]Occult bacteraemia and meningitis were more common in children aged younger than 2 years (21/25, 84%; and 6/8, 75%, respectively). Most pneumonia cases were found in children aged older than 2 years (16/24; 66%).
[b]The presence of rash varied depending on the final diagnosis for the patient (29 of 30 patients (96.7%) with a final diagnosis of sepsis showed rash compared with 2/10 (20%) with meningitis, P < 0.0001).
[c]One of these was methicillin resistant.

- Gangoiti I, Gorostizaga Z, Aranzamendi M, Gomez B, Benito J, Mintegi S. Repeated Emergency Department Visits Among Children with Invasive Bacterial Infections. Pediatr Infect Dis J. 2021 May 1;40(5):e205-e207. doi: 10.1097/INF.0000000000003062. PMID: 33464016

A lo largo de los doce años que duró el periodo de estudio se registraron en el servicio pediátrico de urgencias 601.902 consultas correspondientes a pacientes menores de 14 años, de las cuales 342 fueron diagnosticadas de IBI.

De ellos, 70 no eran previamente sanos y debido a que un paciente entró en parada cardiorrespiratoria en el servicio de urgencias (el paciente falleció por un shock séptico provocado por *S. pyogenes*) no los incluimos en el análisis. En total, el análisis se ha realizado en 271 pacientes previamente sanos.

La edad media fue de 15 meses (entre 5 y 43 meses) y 118 (43,5%) fueron niñas. Ciento noventa y nueve pacientes, el 73,4%, recibieron antibiótico parenteral en su primera visita. La mediana del tiempo entre la primera y la segunda visita de los pacientes que no recibieron antibióticos parenterales en la primera visita fue de 36 horas (intervalo entre el cuartil de 24 a 48 horas) *(ver Table 1)*. En quince pacientes se objetivaron criterios de gravedad: 3 fallecidos y 12 pacientes que desarrollaron secuelas permanentes: 5 neurológicos (fracaso del dispositivo que permite la derivación ventriculoperitoneal y su sustitución, hidrocefalia, sordera y epilepsia), 3 osteoarticulares (necesidad de prótesis, cojera persistente y pequeñas amputaciones), insuficiencia renal crónica en dos pacientes (uno de los cuales requirió trasplante renal), insuficiencia respiratoria restrictiva crónica en dos pacientes y otro paciente con secuela cardiológica grave (necesidad de sustitución de varias válvulas).

De estos 15 pacientes que cumplieron estos criterios de gravedad, siete no recibieron antibióticos en su primera visita (2 muertes, 5 pacientes con secuelas persistentes). El criterio de gravedad se dio más en pacientes que recibieron antibiótico en la segunda consulta (9,8% vs 4%, p = 0,07). La tasa de pacientes que cumplían los criterios de gravedad fue diferente según el tipo de IBI sufrido: 9/61 sepsis (14,8%; IC 95%: 7-26,2), 3/36 meningitis en tres (8,3%; IC 95%: 1,7-22,5), 3/119 infecciones focales invasivas (2,5%; IC 95%: 0,5-7,2) y ningún paciente con criterios de gravedad en el grupo diagnosticado de bacteriemia oculta. Esta tasa no varió en función del intervalo de tiempo entre visitas.

Las tablas y la figura han sido extraídas directamente del artículo original:

Table 1. Characteristics of previously healthy patients with an invasive bacterial infection in relation to the administration or non-administration of parenteral antibiotic on the first visit to the emergency department.

	Parenteral antibiotic administered in the first ED visit		
	Yes; n=199	**No; n=72**	**p**
Age (months)	15 (5-43)	14 (4-42)	n.s
Sex (female)	87 (43.7%)	31 (43.1%)	n.s
Season			
Spring	33 (16.6%)	21 (29.2%)	
Summer	31 (15.6%)	16 (22.2%)	<0.01
Autumn	68 (34.2%)	19 (26.4%)	
Winter	67 (34.2%)	16 (22.2%)	
Fever: yes	195 (98%)	59 (81.9%)	<0.01
Duration of fever (hours)	12 (5-32)	12 (8-48)	n.s
Not well-appearing upon the arrival to the ED	56 (28.1%)	2 (2.8%)	<0.01
No other symptom except fever	58 (29.1%)	33 (45.9%)	0.01
Digestive	44 (22.1%)	11 (15.3%)	
Respiratory tract and ORL	37 (18.6%)	18 (25%)	
Neurologycal	37 (18.6%)	3 (4.2%)	
Exanthema	22 (11.1%)	2 (2.8%)	
Joint/soft tissue	17 (8.5%)	7 (9.7%)	
Normal physical exam	72 (36.2%)	51 (70.8%)	<0.01
Other signs			
Exanthema	50 (25.1%)	6 (8.3%)	
Neurologycal	38 (19.1%)	2 (2.8%)	
Respiratory tract and ORL	28 (14.1%)	11 (15.3%)	
Joint/soft tissue	17 (8.5%)	2 (2.8%)	
Isolated microorganism			n.s.
S. pneumoniae	60 (30.2%)	24 (33.3%)	
N. meningitidis	47 (23.6%)	10 (13.9%)	
S. aureus	20 (10.1%)	14 (19.4%)	
E. coli	31 (15.5%)	7 (9.7%)	
S. agalactiae	11 (5.5%)	1 (1.4%)	
Others	30 (15.1%)	17 (22.3%)	
Final diagnosis			n.s.
Sepsis	47 (23.6%)	14 (19.4%)	
Meningitis	28 (14.1%)	8 (11.1%)	
Occult bacteremia	36 (18.1%)	19 (26.4%)	
Focal infection with bacteremia	88 (44.2%)	31 (43.1%)	
urinary tract infection	28 (14.1%)	4 (5.6%)	
pneumonia	24 (12.1%)	8 (11.1%)	
osteoarticular or soft tissue infection	19 (9.5%)	12 (16.7%	
others	17 (8.5%)	7 (9.7%)	
Severe outcome	8 (4%)	7 (9.7%)	0.07

Analizar el valor de los test sanguíneos habituales (recuento leucocitario, número absoluto de neutrófilos, proteína C reactiva y procalcitonina) que se realizan en pacientes menores de catorce años para su identificación

- Gangoiti I, Fernandez C-L, Gallego M, Gomez B, Benito J, Mintegi S. Markers for invasive bacterial infections in previously healthy children. Am J Emerg Med. 2021 Apr 13;48:83-86. doi: 10.1016/j.ajem.2021.04.018.

A lo largo de los trece años que duró el periodo de estudio se registraron en el servicio pediátrico de urgencias 665.997 consultas correspondientes a pacientes menores de 14 años, de las cuales se diagnosticó IBI a 367 (0,05%). De ellos, 286 (77,9%) fueron pacientes previamente sanos y éstos fueron los pacientes analizados en el artículo.

Ciento sesenta (55,9%) fueron varones y la edad media fue de 14 meses (rango entre 5 y 42 cuartiles). Doscientos pacientes tuvieron un triángulo de evaluación estable (69,9%) al llegar al servicio de urgencias, y en 95 de ellos el examen físico fue normal.

Los diagnósticos finales fueron sepsis 64 (22,4%), meningitis 38 (13,3%), bacteriemia oculta 63 (22,0%) e infección focal invasiva 121 (42,3%) (infección respiratoria 46, urinaria 33, infección osteoarticular o de tejidos blandos 33 y otros 9). Las bacterias aisladas más frecuentes fueron *Streptococcus pneumoniae* 89 (31,1%), *Neisseria meningitidis* 61 (21,3%), *Escherichia coli* 40 (14%) y *Staphylococcus aureus* 36 (12,6%) (el resto 60, 21%).

Doscientos diez pacientes, el 73,4%, recibieron antibiótico parenteral cuando fueron atendidos en su primera visita al servicio de urgencias. En total, fallecieron tres pacientes y 14 sufrieron secuelas permanentes graves.

El recuento de leucocitos y el número absoluto de neutrófilos se realizó en 284 pacientes (99,3%), la proteína C reactiva en 283 (99,0%) y la procalcitonina en 228 (79,7%). La mayoría de los pacientes sin procalcitonina, se reclutaron en los dos primeros años de investigación (fase de entrada de la procalcitonina) o pacientes diagnosticados de neumonía (prueba no protocolizada en el proceso diagnóstico de la neumonía).

En general, 265 (92,7%) tuvieron al menos un valor sanguíneo anormal. La sensibilidad de cada prueba fue: procalcitonina 70,1% (IC 95%: 63,9-76,0), Proteína C reactiva 78,1% (IC 95%: 72,9-82,5), recuento leucocitario 52,8% (IC 95%: 47,0-58,6) y número absoluto de neutrófilos 47,9% (IC 95%: 42,1-53,7). Además, el 85,2% de los recuentos anormales de leucocitos (IC 95%: 78,7-90) correspondió a leucocitosis y el 99,5% del número absoluto anormal de neutrófilos (IC 95%: 97,1-100) a neutrofilia. La leucopenia no fue un hallazgo frecuente, salvo en pacientes diagnosticados de sepsis [22,2% (IC 95%: 13,7-33,9)].

La sensibilidad de cada marcador sanguíneo varió en función del diagnóstico final y la bacteria causante *(ver Figure A y Figure B)*. En el caso de sepsis y meningitis la sensibilidad de la procalcitonina y proteína C reactiva fue mayor; en las infecciones focales invasivas la proteína C reactiva; en el meningococo el de la procalcitonina y en el *S. aureus* la sensibilidad de la proteína C reactiva.

En cuanto a las infecciones neumocócicas, la sensibilidad de los marcadores en sangre no varió en función del estado vacunal. La sensibilidad de cada uno de los marcadores sanguíneos en los niños de 3 a 24 meses diagnosticados de bacteriemia oculta neumocócica fue de 43,5% para la procalcitonina (IC 95%: 25,6-63,2), 48,3% para la proteína reactiva C reactiva (IC 95%: 31,4-65,6), 75,9% para el recuento leucocitario (IC 95%: 57,8-87,8) y 58,6% para el número absoluto de neutrófilos (IC 95%: 40,7-74,5).

En 21 pacientes, el 7,3%, los valores de los biomarcadores fueron normales. La edad media de estos pacientes fue de 2 meses (rango entre el cuartil de 1 a 11 meses) y, salvo en dos pacientes, todos tuvieron un triángulo de evaluación estable cuando fueron atendidos. El diagnóstico final fue de bacteriemia oculta en 11 pacientes (52,4%), meningitis en 4 (19%) e infección focal invasiva en otros 6 (28,6%). Todos evolucionaron bien.

Las figuras han sido extraídas directamente del artículo original.

Figure A. Sensitivity of the tests related to the final diagnosis.

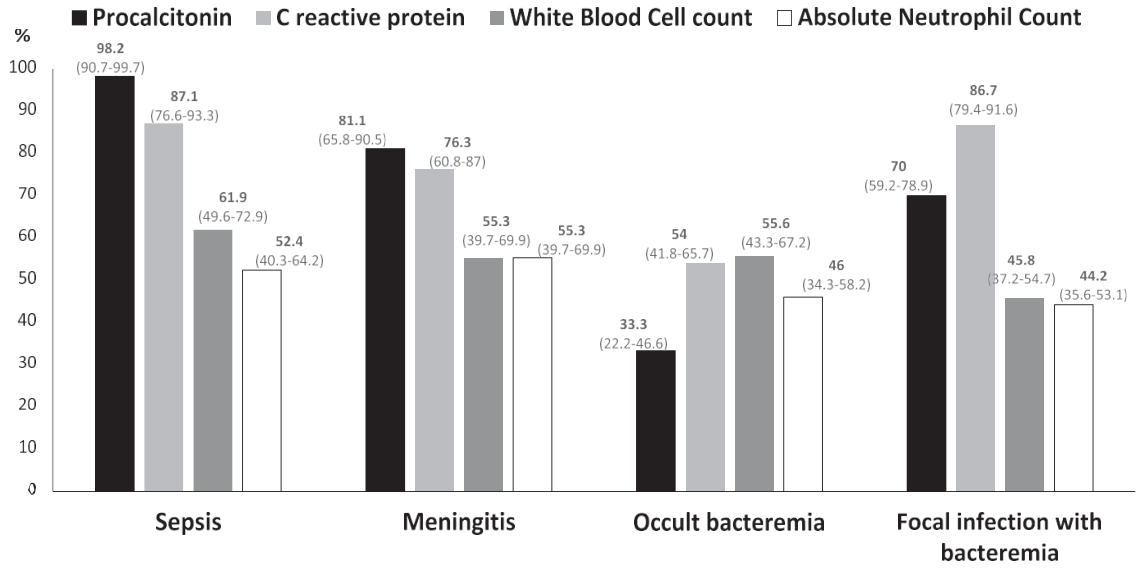
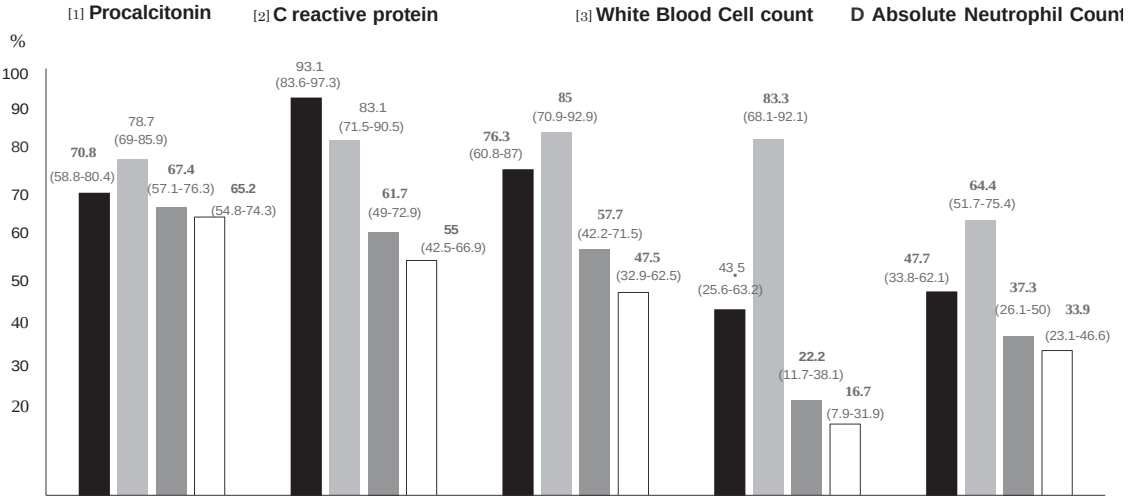


Figure B. Sensitivity of the tests related to the causative bacterium.



Rate of patients with procalcitonin >0.5 ng/ml, C reactive protein>20 mg/L, white blood cell count less than 5000 or higher than 15000/mm3; absolute Neutrophil Count less than 1,500 or higher than 10,000/mm3. 95% Confidence intervals in brackets.

Evaluar la indicación de los test en sangre, en el manejo de niños de 3 a 24 meses de edad con fiebre sin focalidad y estabilidad clínica

- Gangoiti I, Rodriguez E, Zubizarreta A, Benito J, Mintegi S. Prevalence of Occult Bacteremia in Infants With Very High Fever Without a Source. Pediatr Infect Dis J. 2018 Nov;37(11):e271-e273. doi: 10.1097/INF.0000000000001955. PMID: 29462106.

Durante el periodo en el que se realizó la investigación, se obtuvieron 543 hemocultivos entre los lactantes de 3 a 24 meses previamente sanos con fiebre superior a 40,5 ºC *(ver Figure 1)*. Posteriormente, se realizó un análisis en función de si el origen de la fiebre era conocido o no. En los 363 niños con fiebre sin foco, la edad media era de 13,9 ± 4,9 meses y 189 (52,1%) eran mujeres. La vacunación frente al neumococo fue desconocida en 23 (6,3%) y 51 (14%) no había recibido ninguna dosis. La duración de la fiebre fue inferior a 48 horas en 297 (81,8%). Los diagnósticos finales más frecuentes recogidos fueron fiebre sin foco 282 (77,7%); infección urinaria 36 (9,9%); fiebre y exantema 16 (4,4%); neumonía 13 (3,6%) y bacteriemia oculta 4 (1,1%). Todos los pacientes evolucionaron bien.

En este grupo se estimó la prevalencia de bacteriemia oculta del 1,1% (IC 95%: 0-2,2). Tres bacteriemias ocultas fueron neumocócicas (un lactante varón de 16 meses no estaba vacunado contra el neumococo; los otros dos pacientes eran dos niñas de 16 meses y 19 meses con vacunación adecuada) *(ver Supplementary Table)*. La prevalencia de bacteriemia oculta neumocócica se estimó en un 0,82% (IC 95%: 0-1,8%). También se diagnosticó a un niño de 12 meses de bacteriemia oculta por *H. influenzae no tipo b*.

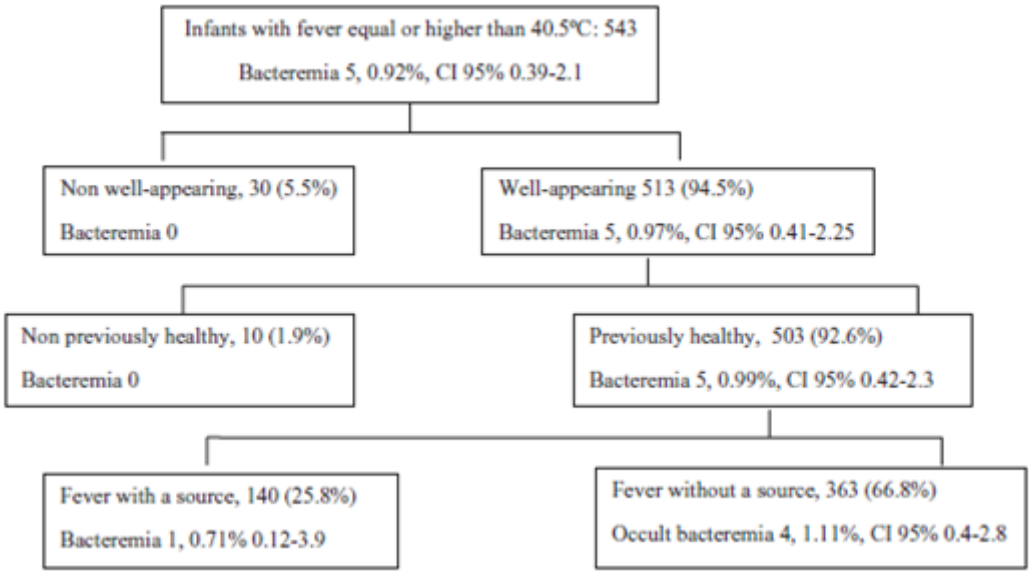
Ningún paciente fue hospitalizado (tres de ellos recibieron una dosis de ceftriaxona intramuscular por protocolo por anomalías en los biomarcadores sanguíneos) y la evolución de todos ellos fue favorable.

Entre esos 289 niños que recibieron al menos una dosis de vacuna antineumocócica, dos pacientes fueron diagnosticados de bacteriemia oculta neumocócica (0,69%; IC 95%: 0-1,6).

Durante el periodo de investigación se recogieron hemocultivos a otros 140 niños previamente sanos; en estos casos el origen podría ser conocido ya que la mayoría de ellos presentaban síntomas relacionados con el aparato respiratorio o síntomas otorrinolaringológicos. En este grupo se identificó un cultivo positivo para *Streptococcus pneumoniae*, paciente de 19 meses diagnosticado de mastoiditis con el calendario vacunal al día.

La figura y la tabla han sido extraídas directamente del artículo original.

Figure 1: Patient Flow-Chart.



Supplementary table. Characteristics of the 4 patients with occult bacteremia.

Age and gender	Pneumo-coccal vaccine	Fever time	WCB	ANC	CRP	PCT	Micro-organism isolation	Antibiotic	Reconsult / destina-tion	Bacteria
12; male	complete	24	25100	20100	57	0.3	Blood culture	Ceftriaxone	No	*H. influenzae*
16; female	Three doses	96	15400	8800	0.2	0.1	Only PCR	No	Yes/ward admition	*S. pneumoniae*
19; female	Three doses	24	11800	8400	34.9	1.1	Only PCR	Ceftriaxone	Called by ED/ward admition	*S. pneumoniae*
16; female	None	1	16200	12100	3.2	4.2	PCR and blood culture	Ceftriaxone + amoxiciline	Telephone control	*S. pneumonia (15c)*

***Age** (months); **fever time** (hours); **WBC**, white blood cells count; **ANC**, absolute neutrophils count; **CRP**, C reactive protein; **PCT**, procalcitonine.*

- Gangoiti I, Zubizarreta A, Elgoibar B, Mintegi S; Infectious Diseases Working Group, Spanish Society of Pediatric Emergencies (SEUP). Occult bacteremia in young children with very high fever without a source: a multicenter study. Pediatr Infect Dis J. 2020 Dec;39(12):e462-e464. doi: 10.1097/INF.0000000000002891.

Durante los dos años que duró la investigación se registraron 344.500 consultas en seis servicios de urgencias pediátricas. De ellos, 203 son lactantes de entre 3 y 24 meses en los que se objetivó una temperatura superior a 40,5 ºC. La edad media fue de 14 ± 4,6 meses y 110 (54,2%) eran varones.

Doscientos pacientes (98,5%) habían recibido al menos una dosis de vacuna frente al neumococo y en 103 casos (50,7%) la evolución de la fiebre fue inferior a 24 horas.

En 31 (15,3%, IC 95%: 11,0-20,9) se diagnosticó una infección bacteriana potencialmente grave: infección urinaria 14 (6,9%), neumonía 11 (5,4%) y bacteriemia 6 (3%).

Tanto la determinación de la proteína C reactiva, procalcitonina, recuento leucocitario como el número absoluto de neutrófilos se realizó en 192 niños. En treinta pacientes (15,6%) los valores fueron normales; entre ellos dos pacientes a los que posteriormente se les diagnosticó una infección de orina y neumonía respectivamente. La punción lumbar se realizó en 3 pacientes (cultivos negativos); la tira reactiva de orina en 169 (83,3%), el urocultivo en 75 (36,9%) y la radiografía de tórax en 97 (47,7%) *(ver Table 1)*.

Todos los niños diagnosticados con bacteriemia oculta tuvieron al menos un valor anormal de algún biomarcador sanguíneo (sensibilidad 100%, IC 95%: 51,7-100; especificidad 16,1%, IC 95%: 11,3-22,4). PPV: 3,7%, IC 95%: 1,5-8,2).

En 3 de los 6 niños diagnosticados de bacteriemia oculta se aisló el neumococo; la prevalencia de bacteriemia oculta neumocócica se estimó en un 1,48% (IC 95%: 0,5-4,3).

La evolución de todos los pacientes que se diagnosticaron de bacteriemia oculta fue buena *(ver Table 2)*.

Las tablas han sido extraídas directamente del artículo original.

Table 1. Epidemiological and clinical characteristics, complementary tests, management and disposition of the patients included (n=204).

Age (in months) *	14 (9.4-18.6)
Sex (male)	111 (54.4%)
Updated vaccination status	200 (98%)
Duration of the fever (in hours)*	42 (8-76)
Blood culture performed	204 (100%)
White blood cell count performed	201 (98.5%)
Absolute neutrophil number performed	201 (98.5%)
Serum C-reactive protein performed	203 (99.5%)
Procalcitonine performed	197 (96.6%)
Urine dipstick performed	170 (83.3%)
Urine culture performed	75 (36.8%)
Chest X-ray performed	97 (47.5%)
Lumbar puncture performed	3 (1.5%)
Administered Antibiotic	126 (61.8%)
Admitted in first consultation	15 (7.4%)
Exitus or sequelae	0

Data are expressed as n and percentage
** Age and evolution time are expressed as median and interquartile range.*

Table 2. Characteristics of patients diagnosed with bacteremia.

	Age (months)	Sex	Fever time (hours)	Updated vaccination/ PCV status	WBC	ANC	CRP	PCT	Antibiotic received	Bacteria
1	13	F	18	Yes/3 doses	18400	9300	75.9	0.23	Yes. Ceftriaxone	*S. pneumoniae*
2	14	M	48	Yes/3 doses	16800	12000	259.1	9.52	Yes. Ceftriaxone	*H. influenza no b*
3	11	F	24	Yes/3 doses	24600	13100	31.83	3.10	Yes. Ceftriaxone	*S. pneumoniae*
4	13	F	18	Yes/2 doses	9400	6100	320	32	Yes. Ceftriaxone	*N. meningitidis*
5	16	M	20	Yes/3 doses	25700	22200	66	5.96	Yes. Ceftriaxone	*S. pneumoniae*
6	23	F	48	Yes/3 doses	18500	11100	77.5	0.19	Yes. Ceftriaxone	*Moraxella spp*

***WBC**, white blood cells count; **ANC**, absolute neutrophils count; **CRP**, C reactive protein; **PCT**, procalcitonine; **F**, Female; **M**, Male.*

Describir la presentación clínica de las infecciones invasivas por *E. Coli* y analizar los posibles perfiles y su posible relación con la gravedad

- Elgoibar B, Gangoiti I, Garcia-Garcia JJ, Hernandez-Bou S, Gomez B, Martinez Indart L, Mintegi S; Bacteremia Study Working Group from the Infectious Diseases Working Group, Spanish Society of Pediatric Emergencies (SEUP). Paediatric *Escherichia col*i bacteraemia presentations and high-risk factors in the emergency department. Acta Paediatr. 2021 Mar;110(3):1032-1037. doi: 10.1111/apa.15549. Epub 2020 Sep 9. PMID: 32815584.

En el periodo en el que se prolongó la investigación se realizaron un total de 3.936.827 consultas en los servicios de urgencias participantes, de las cuales en 1.696 se aisló una bacteria patógena real en la muestra sanguínea de los pacientes (0,04%, IC 95%: 0,04-0,05). En 291 de ellos (17,6%, IC 95%: 15,4-19,0) se aisló *E. coli (características, ver Table 1).*

Los diagnósticos recibidos en este grupo fueron: infección urinaria invasiva en 206 casos (70,8%); bacteriemia oculta 27 (9,3%); sepsis 32 (11%, en tres de los casos se diagnosticó también meningitis); meningitis 5 (1,7%); infección sanguínea asociada a catéter a 6 (2,1%); y el resto 15 (5,1%). Cuarenta y tres casos cumplieron los criterios de gravedad (14,8%, IC 95%: 11,2-19,3), de los que dos fallecieron *(ver Table 2)*.

Los análisis de correspondencia múltiple y el análisis de Clúster identificaron cuatro tipos principales de presentaciones pediátricas de la bacteriemia por *E. coli (ver Table 3)*. Los dos primeros grupos fueron formados por niños previamente sanos de menos de un año y buen aspecto, relacionados con infección urinaria invasiva siendo la principal diferencia la edad y el sexo. En el primer grupo predominaban los niños menores de tres meses y en el segundo grupo las niñas de 3 a 12 meses. La evolución general fue favorable, con tasas

de gravedad del 5,3% y 3,1%, respectivamente. El tercer grupo estaba formado en gran parte por pacientes no sanos con más de 12 meses de edad. En el último grupo había niños de diferentes edades, un tercio no era previamente sano y la proporción de pacientes no estables según el triángulo de evaluación era mayor que el resto de grupos. Estos dos últimos grupos no estaban tan relacionados con las infecciones de orina y las tasas de gravedad fueron significativamente superiores, 15% y 50,9% respectivamente ($p < 0,01$). Los dos pacientes fallecidos se integraron en el último grupo.

Ocho niños fueron diagnosticados de meningitis bacteriana (en tres de ellos también se diagnosticó sepsis), todos ellos menores de 5 meses *(ver Table 4)*. La tasa de meningitis que se detectó en las bacteriemias causadas por *E. coli* menores de un mes fue del 9,4% y entre los niños de un mes y dos meses fue del 2,6%. La meningitis se diagnosticó en un solo paciente mayor de dos meses.

Las tablas han sido extraídas directamente del artículo original.

Table 1. Epidemiological and clinical characteristics, complementary tests, management and disposition of the patients with *E. coli* bacteremia.

Age (in months) *	3 (1-11)
Sex (female)	131 (45%)
Non- previously healthy patients	67 (23%)
Immunosuppression	27 (9.3%)
Patients with multiorgan syndromes or systemic illness	16 (5.4%)
Serious kidney or urinary malformations	13 (4.5%)
Presence of a mechanical device	7 (2.4%)
Invasive diagnostic or therapeutic procedure in the previous 10 days	4 (1.4%)
Duration of the fever (in hours) *	12 (3-24)
Temperature upon arrival to the emergency department (°C) **	37.9 ± 1.0
Well appearing upon arrival to the emergency department	244 (83.8%)
No findings in the physical examination	226 (77.7%)
Urine culture performed	263 (90.4%)
Lumbar puncture performed	71 (24.4%)
Chest X-ray performed	33 (11.3%)
Administered Antibiotic	284 (97.6%)
Admission toward /Intensive Care Unit	255 (87.6%)

Data are expressed as n and percentage.
***** *Age and evolution time are expressed as median and interquartile range.*
****** *Temperature is expressed as mean ± standard deviation.*

Table 2. Number of patients with each severity criteria.

Severity criteria	N (%)
Sepsis	32 (11.0%)
Admission to the Intensive Care Unit *	22, 7.6%
Acute complications	8, 2.7%
Meningitis	8, 2.7%
Sequelae	7, 2.4%
Death	2, 0.7%

Data are expressed as n and percentage.
Twenty patients (6.9%) presented a single severity criteria; Sixteen patients (5.5%) presented two severity criteria; Seven patients (2.4%) presented three or more severity criteria.
***** *There are no patients with this severity criteria exclusively.*

Table 3. Main types of pediatric *E. coli* bacteremia presentations.

Variable		A (n=113, 38.8%)	B (n=65, 22.3%)	C (n=60, 20.6%)	D (n=53, 18.2%))	p value
Sex	Female	21 (18.6%)	57 (87.7%)	36 (60%)	17 (32.1%)	<0.001
Age	<3 months	95 (84.1%)	10 (15.4%)	3 (5%)	24 (45.3%)	<0.001
	3-12 months	18 (15.9%)	55 (84.6%)	6 (10%)	15 (28.3%)	
	>12 months	0	0	51 (85%)	14 (26.4%)	
Previously healthy	No	3 (2.7%)	0	47 (78.3%)	17 (32.1%)	<0.001
Fever*	Yes	88 (77.9%)	65 (100%)	58 (96.7%)	41 (77.4%)	<0.001
Other symptoms	Yes	24 (21.2%)	40 (61.5%)	30 (50%)	45 (84.9%)	<0.001
PAT**	Altered appearance	1 (0.9%)	1 (1.5%)	2 (3.3%)	35 (66%)	<0.001
	Altered Circulation	1 (0.9%)	0	1 (1.7%)	18 (34%)	
	Altered breathing	0	0	0	6 (11.3%)	
Physical exam	Altered	7 (6.2%)	5 (7.7%)	8 (13.3%)	45(84.9%)	<0.001
Associated UTI	Yes	96 (85%)	64 (98.5%)	30 (50%)	16 (30.2%)	<0.001

***** *Temperature higher than 38ºC at home and/or at the emergency department.*
****Pediatric assessment triangle.*
Data are expressed as n and %. The p values demonstrate the differences between groups among the analyzed variables.

Table 4. Rate of associated meningitis in febrile infants with *E. coli* bacteremia related to the age.

Group of age	Rate of bacterial meningitis
< 1 month old	6/64, 9.4%, 95% CI 4.4-19
1 <= months < 2	1/38, 2.6%, 95% CI 0.5-13.5
2 <= months < 3	0/30, 0, 95% CI 0-11.3
3-24 months old	1/107, 0.9%, 95% CI 0.2-5.1

Data are expressed as n, percentage and confidence interval.
***CI**, confidence interval.*

Describir la presentación clínica de la infección invasiva por estreptococo del grupo B y analizar su posible relación con la gravedad

- Ecclesia FG, Alonso Cadenas JA, Gómez B, Gangoiti I, Hernández-Bou S, de la Torre Espí M; Bacteremia Study Working Group from the Infectious Diseases Working Group, Spanish Society of Pediatric Emergencies. Late-onset Group B *Streptococcus* Bacteremia Evaluated in the Pediatric Emergency Department and Risk Factors for Severe Infection. Pediatr Infect Dis J. 2022 Jun 1;41(6):455-459. doi: 10.1097/INF.0000000000003520. Epub 2022 May 6. PMID: 35446825.

Los datos generales son los extraídos del mismo artículo anterior. En total el estreptococo del grupo B creció en 134 pacientes (7,9%, IC: 6,6-9,2) y en 118 (88,1%) se definió la bacteriemia tardía por estreptococo del grupo B *(características, ver Table 1)*.

En 17 pacientes (14,4%) se identificó algún factor de riesgo; la colonización materna o estado de colonización desconocido, en 10 casos; en 5 casos el niño fue prematuro y dos pacientes presentaron ambos factores de riesgo. Dos niños prematuros cuya situación de colonización materna era desconocida no recibieron antibioterapia intraparto y ambos desarrollaron una sepsis tardía.

En cuanto a los valores de los biomarcadores, el recuento leucocitario y el número absoluto de neutrófilos se realizó en todos los pacientes, la proteína reactiva C en 117 (99,2%) y la procalcitonina en 93 (78,8%). En total, 91 (77,1%) tuvieron al menos un valor anormal. La sensibilidad de cada prueba fue: Procalcitonina 80,6% (IC 95%: 71,1-88,1), recuento leucocitario 44,1% (IC 95%: 34,9-53,5), número absoluto de neutrófilos 34,7% (IC 95%: 26,2-44,1) y Proteína C reactiva 27,4% (IC 95%: 19,5–36,4). En cuanto a la sensibilidad de los análisis de los diferentes marcadores sanguíneos para el diagnóstico de la infección grave no se encontraron diferencias estadísticamente

significativas, aunque se detectaron valores superiores a 0,5 ng/ml de procalcitonina en las infecciones graves *(ver Table 2)*.

El diagnóstico final fue sepsis en 66 pacientes (55,9%; 11 de ellos con meningitis), bacteriemia oculta 40 (33,9%), meningitis 8 (6,8%); infección focal invasiva 4 (3,4%; 2 infecciones osteoarticulares y 2 infecciones urinarias).

Globalmente, 74 (62,7%) sufrieron una infección grave, solamente 15 de ellos presentaron un triángulo de evaluación estable cuando fueron atendidos en el servicio de urgencias. Basándose en el modelo multivariante, el único factor de riesgo relacionado con la infección grave que alcanzó significancia estadística fue la situación no estable basada en el triángulo de evaluación pediátrica *(ver Table 3)*.

La hospitalización se realizó en 115 pacientes, 35 de ellos (29,7%) en la UCI. El modelo multivariante que investigó los factores de riesgo relacionados con el ingreso en la UCI sólo señaló a la leucopenia *(ver Table 4)*.

En seis pacientes la evolución no fue buena (5,1%), todos tuvieron complicaciones agudas graves (5,1%), dos sufrieron secuelas persistentes y otros dos fallecieron Los seis pacientes fueron menores de 26 días, no estaban estables según el triángulo y los valores de procalcitonina fueron altos (con intervalos de 4,7-100 ng/ml); entre los cuales la leucopenia se observó en cuatro pacientes (intervalo 2300-9200 leucocitos/mm3).

Las tablas han sido extraídas directamente del artículo original.

Table 1. Epidemiologic and clinical features, management, and outcomes of infants with late-onset disease Group B *Streptococcus*.

	Late-onset disease (N=118)
Sex (males) - *n (%)*	68 (57.6)
Age – *days, median (IQR)*	28 (16-43)
Normal PAT upon arrival - *n (%)*	56 (47.5)
Reported symptoms – *n (%)*	
Fever	86 (72.9)
Fever without a source	29 (24,6)
Fever with other symptoms	57 (48.3)
Irritability	38 (32.2)
Somnolence, lethargy	20 (16.9)
Respiratory symptoms	13 (11.0)
Others[1]	16 (13.6)
Fever, time since onset – *hours, median, (IQR)*	2 (0-4)
Normal PE – *n (%)*	56 (47.5)
Discharge to home *n (%)*	3 (2.5)
Admission *n (%)*	
Ward	80 (67.8)
PICU	35 (29.7)
<u>Outcomes</u> *n (%)*	
Acute complications	6 (5.1)
Sequelae	2 (1.7)
Death	2 (1.7)

*[1]Digestive, local pain. **CI**, confidence interval; **IQR**, interquartile range; **PAT**, Pediatric Assessment Triangle; **PE**, physical examination; **PICU**, pediatric intensive care unit.*

Table 2. Epidemiologic features, clinical characteristics, laboratory test results, and management with severe and non-severe infections.

	Non-severe infection[1] (n=44)	Severe infection[2] (n=74)	p-value
Sex (Males) - *n (%, 95% CI)*	28 (63.6, 47.8-77.6)	40 (54.1, 42.1-65.7)	n.s.
Risk factors for GBS - *n (%, 95% CI)*	3 (6.8, 1.4-18.7)	14 (18.9, 10.7-29.7)	n.s.
Age – *median days (IQR)*	28.5 (16-42.5)	28 (15-43)	n.s.
Normal PAT upon arrival - *n (%, 95% CI)*	41 (93.2, 81.3-98.6)	15 (20.3, 11.8-31.2)	**<0.001**
Normal PE upon arrival – *n (%, 95% CI)*	31 (70.5, 54.8-83.2)	25 (33.8, 23.2-45.7)	**<0.001**
Admission Ward PICU	 37 (84.1, 69.9-93.4) 4 (9.1, 2.5-21.7)	 43 (58.1, 46.1-69.5) 31 (41.9, 30.5-53.9)	**<0.001**
WBC – *(median /mm^3, IQR)* **- sensitivity (WBC <5,000 or >15,000/mcL)**	11,840 (8,300-16,455) 38.6% (95 % CI; 24.4-54.5%)	7,300 (4,100-11,200) 35.1% (95% CI: 24.4-47.1%)	**<0.001**
ANC - *(median /mm^3, IQR)* **- sensitivity (ANC <1,500 or >10,000/mcL)**	6,310 (4,500-10,598) 34.1% (95% CI: 20.5-49.9%)	4,530 (1,975-8,300) 35.1% (95% CI: 24.2-47.1%)	**0.01**
CRP – *(median mg/L, IQR)* **- sensitivity (CRP ≥20 mg/L)**	5.5 (2.1-18.0) 23.3% (95% CI: 11.8-38.6%)	7.7 (3.6-24.0) 29.7% (95% CI: 19.7-41.5%)	n.s.
PCT – *(median ng/ml, IQR)* **- sensitivity (PCT ≥0.5 ng/ml)**	1.7 (0.4-6.5) 71.8% (95% CI: 55.1-85.0%)	3.5 (0.7-21.8) 87.0% (95% CI: 75.1-94.6%)	n.s.

*[1]Included: occult bacteremia and focal infection (osteoarticular and urinary tract infection); [2]Included: sepsis/septic shock, meningitis, and sepsis/septic shock with associated meningitis; **CI**: confidence interval; **GBS**, Group B Streptococcus; **PAT**, Pediatric Assessment Triangle: **PE**, physical examination; **WBC**, white blood cell count; **ANC**, absolute neutrophil count; **CRP**, C-reactive protein; **PCT**, procalcitonin; **n.s.**, not significant.*

Table 3. Multivariate analysis to identify independent risk factors for severe infection.

Risk factors for severe infection	OR	95% CI	p-value
Age (days)	0.9	0.95-1.02	n.s.
Maximum temperature (ºC)	0.7	0.4-1.2	n.s.
Altered PAT upon arrival (%)	43.6	8.1-235.7	**<0.001**
Altered PE upon arrival (%)	1.5	0.3-6.9	n.s.
WBC – (/mm^3)			
Group 1: <5,000	1.5	0.05-45.3	n.s.
Group 2: 5,000-15,000	Reference	Reference	
Group 3: >15,000	5.1	0.6-45.4	n.s.
ANC – (/mm^3)			
Group 1: <1,500	1.2	0.02-86.1	n.s.
Group 2: 1,500-10,000	Reference	Reference	
Group 3: >10,000	0.2	0.02-2.3	n.s.
CRP – (mg/L)	1.0	0.9-1.0	n.s.
PCT – (ng/ml)	1.0	0.9-1.1	n.s.

***PAT**, Pediatric Assessment Triangle; **PE**, physical examination; **WBC**, white blood cell count; **ANC**, absolute neutrophil count; **CRP**, C-reactive protein; **PCT**, procalcitonin; **OR**, odds ratio; **CI**, confidence interval; **n.s.**, not significant.*

Table 4. Multivariate analysis to identify independent risk factors for pediatric intensive care unit admission.

Risk factors for PICU admission	OR	95% CI	p-value
Age (days)	0.9	0.9-1.0	n.s.
Maximum temperature (ºC)	1.0	0.3-3.9	n.s.
GBS infection risk factors (%)	1.4	0.3-6.7	n.s.
Altered PAT upon arrival (%)	7.1	0.9-56-5	n.s.
Altered PE upon arrival (%)	3.2	0.5-21.3	n.s.
WBC – (/mm^3)			
Group 1: <5,000	11.6	1.5-91.4	**0.019**
Group 2: 5,000-15,000	Reference	Reference	
Group 3: >15,000	0.08	0.01-2.2	n.s.
ANC – (/mm^3)			
Group 1: <1,500	0.8	0.1-8.1	n.s.
Group 2: 1,500-10,000	Reference	Reference	
Group 3: >10,000	7.0	0.3-156.7	n.s.
CRP – (mg/L)	1.1	0.999-1.14	n.s.
PCT – (ng/ml)	1.0	0.968-1.04	n.s.

***GBS**, Group B Streptococcus; **PAT**, Pediatric Assessment Triangle; **PE**, physical examination; **WBC**, white blood cell count; **ANC**, absolute neutrophil count; **CRP**, C-reactive protein; **PCT**, procalcitonin; **OR**, odds ratio; **CI**, confidence interval; **n.s.**, not significant.*

Objetivos secundarios. Describir el impacto de una pandemia no esperada en la epidemiología de las IBI identificadas en un servicio de urgencias pediátrico

- Martin-Irazabal G, Gangoiti I, Gomez B, Lizarraga L, Mintegi S. Impact of the COVID-19 pandemic on pediatric invasive bacterial infections. An Pediatr (Engl Ed). 2023 Mar;98(3):228-229. doi: 10.1016/j.anpede.2023.01.013. Epub 2023 Feb 20. PMID: 36813615; PMCID: PMC9940794.

En los dos periodos de tiempo que duró el estudio se registraron 269.105 consultas en el servicio pediátrico de urgencias correspondientes a pacientes menores de 14 años (153.736 en prepandemia, 4.270 consultas/mes, y 115.369 en pandemia, 3.393 consultas/mes; diferencia 20,5%) y en 119 pacientes previamente sanos se diagnosticó una IBI. En el periodo prepandemia, se diagnosticaron 70 IBI y 49 durante la pandemia. Durante la pandemia, la probabilidad de diagnosticar IBI en un paciente previamente sano varió considerablemente: la probabilidad fue mayor en 2020; en 2021, con medidas menos restrictivas y aumento de las consultas, el número de IBI por mes fue menor que el año anterior y la probabilidad de que el paciente previamente sano fuera diagnosticado con una IBI también. El 2022 presentó una situación similar a la época anterior a la pandemia. Por otro lado, en cuanto a los responsables de IBI durante la pandemia, se produjeron cambios significativos; desapareció la *N. meningitidis* en 2021, mientras que en 2022 hubo un incremento importante de *S. pneumoniae* (9/22; 40,9% de las IBI diagnosticadas). En niños menores de tres meses, el estreptococo del grupo B fue la principal causa de IBI durante la pandemia (33,3%) vs. *E. coli* (50%) en prepandemia ($p < 0,01$) *(ver Tabla 1)*.

La tabla ha sido extraída directamente del artículo original.

Tabla 1. Episodios totales e infecciones bacterianas invasivas (IBI) registradas en el servicio de urgencias pediátrico (SUP) antes y durante la pandemia por coronavirus SARS-CoV-2.

	Episodios en SUP	Episodios/ mes	IBI	IBI/mes	IBI/episodios	Bacterias más prevalentes
PRE-PANDEMIA	153.736	4.270	70	1,94	**1 IBI / 2196 episodios**	*S. pneumoniae* (18,6%) *N. meningitidis* (18,6%) *S. aureus* (17,1%) *E. coli* (15,7%) *S. agalactiae* (5,7%)
PANDEMIA						
2020	21.746	2.175	19	1,90	**1 IBI / 1144 episodios ***	*S. pneumoniae* (28,6%) *S. aureus* (20,4%) *N. meningitidis* (10%) *S. agalactiae* (10%) *E. coli* (10%)
2021	39.880	3.323	8	0,67 *	**1 IBI / 4985 episodios ***	
2022	53.743	4.478	22	1,83	**1 IBI / 2443 episodios**	

** p<0.01, al comparar con el periodo pre-pandemia.*

DISCUSIÓN

Todos los artículos recogidos en esta tesis no hacen más que subrayar la importancia de las ideas que aparecían en la hipótesis. La investigación y monitorización continua de los pacientes diagnosticados de IBI parece una actividad imprescindible para caracterizar a los que pueden consultar en un Servicio de Urgencias, conocer las condiciones en las que llegan, el rendimiento que se puede obtener de la anamnesis, examen físico o pruebas complementarias, prever su evolución e identificar los factores de riesgo que pueden relacionarse con las evoluciones más tórpidas. La atención de calidad al niño, niña y adolescente que pueda sufrir una IBI dependerá, entre otras cosas, de todo lo que hemos dicho anteriormente. En definitiva, los cambios sanitarios y sociales vividos en nuestra sociedad, ponen de manifiesto la importancia de configurar sistemas de observación y vigilancia de infecciones graves y de fortalecer los ya existentes. Aunque no haya sido un objetivo de esta tesis, el impacto de la pandemia COVID en la epidemiología de las IBI que se han diagnosticado en nuestro entorno creemos que confirma todo lo anterior.

Uno de los hallazgos más destacados de los trabajos de investigación recogidos en esta tesis es que la IBI es un hallazgo inusual entre las consultas que se atienden en un SUP (tasa de 0,04-0,05%, es decir, aproximadamente uno de cada 2500 niños que acuden a un SUP) y que en gran parte aparecen en pacientes previamente sanos. Entendiendo que trabajamos en un sistema de salud con accesibilidad universal, identificar de la mejor manera posible casos tan aislados, pero tan graves es todo un reto. Además, hay que tener en cuenta que los casos de muchos tipos de IBI han disminuido considerablemente, gracias a las campañas de vacunación entre otras causas. Este descenso también ha disminuido la exposición de los propios médicos a pacientes con sospecha de una IBI, dificultando el diagnóstico.

Es cierto que la evolución de los pacientes pediátricos que han sufrido una IBI es, en general buena, pero las muertes y las secuelas graves persistentes no son infrecuentes. En el estudio que tenía como objetivo caracterizar a los niños que han sufrido IBI, los pacientes identificados como inestables con el TEP a su llegada a urgencias, que además de la fiebre presentaron otros síntomas y aquellos que habían sido atendidos por debajo de las primeras 24 horas tras el inicio de la fiebre evolucionaron peor. Sin embargo, las características clínicas, el diagnóstico y la evolución de estos pacientes fue diferente según la bacteria patógena aislada. En este estudio, el patógeno aislado con más frecuencia fue *S. pneumoniae*, principal causa de bacteriemia oculta y neumonía invasiva y, junto con *N. meningitidis*, la principal causa de shock y meningitis. Entre las IBI neumocócicas, la bacteriemia oculta y la meningitis se identificaron con mayor frecuencia en niños menores de dos años y en los mayores de esta edad, las neumonías. Por otra parte, más de la mitad de los niños con IBI que presentaron secuelas y en algunos casos fallecimiento, fueron debidos a *S. pneumoniae*, lo que justifica que las acciones y recursos preventivos sean imprescindibles[194]. Con relación a la prevención, es destacable que un alto porcentaje de los serotipos de los neumococos aislados en nuestro estudio estaría incluido dentro de los presentes en la vacuna antineumocócica trecevalente (PCV13), tal y como ya ha sido señalado por otros investigadores[197]. Por otra parte, se ha documentado una disminución de la prevalencia global de *S. pneumoniae* tras la implantación del PCV13, aunque se especula que este descenso podría haber sido mayor si la cobertura vacunal de la población hubiera sido más amplia[137]. Sin embargo, son cada vez más las voces de expertos alertando que la sustitución de serotipos se está dando más rápido que con la vacuna antineumocócica heptavalente, sobre todo con el aumento del serotipo 8[198]. Por otro lado, en los últimos años se ha observado que el serotipo 3, incluido en la vacuna PCV13, es en la actualidad el segundo principal causante de infecciones neumocócicas

invasivas[198], creciendo la preocupación de que este serotipo haya adquirido la capacidad de superar la protección que otorga esta vacuna[199]. Se espera que las nuevas vacunas antineumocócicas ya comercializadas o que se vayan a elaborar, proporcionarán nuevamente esta protección. Sin embargo, y como ya se ha mencionado en la introducción, la información al respecto va cambiando[200], destacando de nuevo la importancia de los sistemas de investigación y monitorización.

Como ya ha sido señalado por otros investigadores[46] *N. meningitidis* fue la causa principal de la sepsis y se relacionó con una mayor gravedad respecto a otras IBI. Sin embargo, nuestro estudio muestra una serie de particularidades. Por una parte, llama la atención la elevada tasa de infecciones meningocócicas en los niños mayores de dos años, teniendo en cuenta que la mayor incidencia de infección meningocócica se refiere habitualmente entre los niños menores de un año[201]. Además, a diferencia de otras series[202,203], un porcentaje significativo de pacientes no desarrollaron rash cutáneo, especialmente en aquellos en los que se diagnosticó meningitis meningocócica, siendo este un aspecto relevante en el momento de elegir la antibioterapia empírica más adecuada[204]. Finalmente, la evolución de los pacientes que sufrieron infección meningocócica fue mejor que la descrita en la literatura[205]. Probablemente estas especiales características de los pacientes en nuestro estudio se deban a posibles diferencias en la prevalencia de algunos serogrupos de meningococo y a las características de nuestro entorno sanitario con un fácil acceso a los servicios de urgencias hospitalarios, lo que condiciona que los niños y sus familias consulten con mayor prontitud.

Como ya señala la literatura, en nuestro estudio el *S. aureus* fue la bacteria más frecuentemente aislada en niños mayores y se relacionó con infecciones osteoarticulares o de tejidos blandos, siendo mayor la duración de los síntomas, antes de la consulta.

Cuando se completó la base de datos y, sobre todo, cuando se realizó el análisis para este artículo, no se recogieron datos para conocer la tasa de *S. aureus* resistente a meticilina adquirido en la comunidad, aspecto que hoy es motivo de preocupación. Las tasas publicadas en nuestro entorno[77] son elevadas y por tanto deberá ser tenido en cuenta a la hora de seleccionar el antibiótico más adecuado.

En el análisis de las infecciones tardías causadas por el estreptococo del grupo B, derivadas del registro multicéntrico de hemocultivos, llama la atención que el 5% tuvo graves consecuencias y que la tasa de mortalidad fue el 2%. El único factor de riesgo que se identificó para desarrollar una infección grave fue la inestabilidad detectada mediante el triángulo de evaluación pediátrica, lo que parece además estar relacionado con una peor evolución. Este subanálisis se ha realizado en una de las mayores series prospectivas que ha estudiado la infección tardía por el estreptococo del grupo B en niños de 7 a 89 días y, en comparación con los datos publicados sobre bacteriemias causadas por *E. coli*, parece que son infecciones más graves, ya que provoca sepsis y meningitis con más frecuencia[81], siendo además más frecuentes las complicaciones agudas y las muertes.

En el subanálisis realizado sobre las infecciones invasivas por *E. coli,* se identificaron cuatro grupos con diferente presentación clínica. El grupo de niños menores de un año y, sobre todo, el de menores de tres meses, se relacionó con mayor frecuencia con infecciones urinarias invasivas y la inestabilidad inicial se asoció con mayor gravedad. Por eso, es imprescindible tener un alto índice de sospecha de enfermedad bacteriana invasiva de mayor gravedad cuando estamos ante estos pacientes. En resumen, las características típicas de las infecciones bacterianas que sufren los lactantes más pequeños (en el caso de ambas bacterias) son bastante similares; consultan muy temprano, sus signos y síntomas normalmente no son demasiado significativos y están estables. Estos

hallazgos ponen de manifiesto la importancia de la aproximación inicial utilizando el triángulo pediátrico de evaluación, especialmente cuando se detecta inestabilidad, como hemos señalado muy relacionada con una mayor gravedad y peor pronóstico.

Por otro lado, el estreptococo del grupo B en un número significativo de pacientes se aisló no sólo en el hemocultivo sino también en el LCR. Esto confirma la recomendación de punción lumbar, si no se realizó en el estudio inicial, cuando se identifique esta bacteria en la muestra de sangre en los niños menores de 3 meses[206].

Por otro lado, los niños menores de 28 días con infección urinaria por *E. coli* son los que presentan mayor riesgo de padecer bacteriemia[51]. En los últimos años se ha intentado identificar pacientes diagnosticados con una posible infección por vía urinaria con bajo riesgo de bacteriemia y por tanto susceptibles de manejo ambulatorio[207,208]. De hecho, en diferentes estudios se ha señalado que la evolución de estos niños que han sido tratados con antibioterapia adecuada ha sido buena y segura, independientemente de que hayan asociado o no bacteriemia[209]. Sin embargo, en nuestro estudio, todos los niños con meningitis bacteriana, salvo uno, eran menores de dos meses y el 10% de los menores con bacteriemia por *E. coli* sufrieron meningitis. El riesgo de meningitis asociado a la infección urinaria ha sido publicado en niños menores de un mes[210]. Nuestro estudio corrobora la recomendación de una punción lumbar en el niño menor de dos meses en caso de identificación de *E. coli* en el hemocultivo. Por otra parte, la gravedad de la infección invasiva causada por *E. Coli* fue mayor en los lactantes no previamente sanos y sobre todo en los que se identificó inestabilidad aplicando el triángulo de evaluación pediátrica, por lo que el manejo a realizar con estos niños debe ser muy cuidadoso.

En el primer estudio que forma parte de esta la tesis, nos llamó la atención el porcentaje elevado de pacientes que realizaron alguna visita previa a urgencias antes de realizar el

diagnóstico de IBI. Aunque este porcentaje fue algo inferior al comunicado anteriormente[24], la tasa de mortalidad y la proporción de secuelas de los pacientes diagnosticados en la segunda visita fueron superiores, aunque estadísticamente no significativas. Se ha sugerido que la progresión hacia la sepsis o meningitis del niño con fiebre y buen aspecto es algo impredecible, por lo que la evaluación clínica estandarizada que se realiza en la primera visita debería ser suficiente[25]. La dificultad para el diagnóstico en fases muy precoces de las IBIs, puestas de manifiesto en dos de los estudios que forman parte de esta tesis, aconsejan que, tras la primera atención de un niño con fiebre en el servicio de urgencias, existe la necesidad de un seguimiento posterior por parte de un médico de atención primaria, además de explicar con claridad las recomendaciones sobre los cuidados a realizar y los síntomas de alarma a vigilar por los cuidadores en casa.

El estudio realizado por Vaillancourt et al encontró que la evolución final de los pacientes que desarrollaron sepsis no fue diferente entre quienes tuvieron una o más visitas previas al diagnóstico de la enfermedad. Aunque discutible, una editorial posterior argumentó que probablemente la sepsis y la meningitis no estaban presentes en la primera visita, por lo que no era posible realizar el diagnóstico[25]. Las recomendaciones sobre el manejo de pacientes con IBI, y en concreto en el caso de la sepsis, subrayan la importancia de su identificación precoz en pacientes con signos o síntomas que podrían indicar una posible infección. Es importante señalar que el retraso en la administración de antibióticos influye en la evolución de la sepsis y la meningitis[41].

Es posible que el examen físico en una consulta muy temprana no dé información que permita sospechar una IBI. Esto puede justificar que, en dos tercios de los pacientes que no fueron diagnosticados en la primera visita en nuestra serie, no se indicaran pruebas complementarias. Las guías de práctica clínica recomiendan que para la identificación

precoz de la sepsis es necesario un instrumento o batería de recursos. Pero para que estas herramientas sean eficaces, deberían aplicarse en todos los pacientes que consultan en un servicio de urgencias y la mayoría se basan en el uso de parámetros clínicos más que en la realización de pruebas de laboratorio[211]. Sin embargo, muchos pacientes que consultan por fiebre tienen alguna de las señales de alarma que pueden sugerir sepsis, pero estas señales también están presentes en muchos de los pacientes con infecciones virales autolimitadas. Por este motivo, la comunidad científica es consciente de que la implantación de estas herramientas de cribaje supone un claro aumento de recursos, fatiga y iatrogenia[212], teniendo en cuenta además que el paciente pediátrico puede mantener parámetros hemodinámicos normales en las fases iniciales de la sepsis.

Por todo lo expuesto, es importante realizar pruebas complementarias en el paciente que muestre señales sugestivas de sepsis y también en aquellos pacientes en los que lo recomienden los protocolos de manejo clínico. Con la ayuda de los niveles de los biomarcadores en sangre utilizados habitualmente en un servicio de urgencias se ha tratado de determinar el perfil del paciente con riesgo de IBI.

De hecho, la mayoría de los pacientes previamente sanos con IBI confirmada microbiológicamente, mostraron al menos la alteración de uno de los biomarcadores más frecuentemente analizados. Hemos explicado, sin embargo, que la sensibilidad de estos marcadores varía en función de la bacteria causante aislada y del diagnóstico final del paciente. En general, la procalcitonina y la proteína C reactiva aumentaron más que otros marcadores clásicos, sobre todo en pacientes con enfermedad grave como sepsis o meningitis, pero su sensibilidad fue escasa en los que padecían bacteriemia oculta.

Por su parte, la procalcitonina ofrece una serie de ventajas para la identificación de pacientes con IBI[99], meningitis[130] y la infección meningocócica invasiva[205]. Parece que

la proteína reactiva C es más útil cuando se evalúa al paciente susceptible de infección focal invasiva, especialmente en las infecciones cutáneas y de tejido blando y en las infecciones osteoarticulares causadas sobre todo por *Staphylococcus aureus*. En el caso del estreptococo del grupo B el único factor de riesgo de ingreso en la UCI fue la leucopenia; pero no fue un factor de riesgo de secuelas graves, como ya se ha dicho anteriormente[213,214].

Los niños con bacteriemia oculta merecen especial atención. Estos pacientes están estables y presentan solamente fiebre sin otros signos ni síntomas. En nuestra serie la procalcitonina no parece muy rentable en el caso de la bacteriemia oculta neumocócica, tal y como se informó anteriormente sobre el rendimiento de la proteína C reactiva[18]. En estos pacientes los marcadores clásicos serían más útiles, y entre ellos el recuento de leucocitos. Este hallazgo es relevante, ya que como se ha dicho anteriormente, la realización de análisis de sangre sin una clara indicación a la hora de evaluar a un niño con fiebre sin focalidad, o el añadir más marcadores, pueden aumentar el número de pacientes que reciben antibióticos y otros manejos innecesarios, en lugar de conseguir una mejor identificación del niño con una IBI[19]. Sin embargo, sí parece recomendable realizar pruebas si la fiebre es muy elevada.

En la discusión no podemos olvidar cómo la pandemia que hemos vivido ha cambiado los hábitos de vida, el comportamiento humano y todos los parámetros relacionados con la salud y que todo ello debería haber supuesto un aprendizaje para futuras situaciones similares.

Durante la pandemia, la probabilidad de que un paciente previamente sano que consultaba en urgencias tuviera una IBI varió mucho. Sin embargo, no hemos encontrado explicación al descenso en el número absoluto de pacientes que se diagnosticaron de IBI en el segundo

año de la pandemia. Consideramos importante que los médicos que atienden a niños con fiebre sin focalidad conozcan esta información, ya que se podría pensar erróneamente que con una menor transmisibilidad de patógenos respiratorios, la posibilidad de diagnosticar IBI en un paciente que es atendido en urgencias es menor. Además, la modificación de la prevalencia de IBI puede afectar al rendimiento de los diferentes scores de predicción clínica o de otros instrumentos y recursos utilizados para identificar a los pacientes con IBI. Cuando las medidas de protección fueron más estrictas, se produjo prácticamente la desaparición total de la infección meningocócica invasiva, con una disminución en España de la tasa de incidencia hasta 0,14 casos en por cada 100.000 habitantes[67]. En otros países se vivieron situaciones similares[68,215]. Posteriormente, tras la relajación de las medidas adoptadas durante la pandemia se han publicado datos en algunos países que indican un aumento de la enfermedad meningocócica, como el Reino Unido[216]. En nuestro caso, en 2022 se observó un notable rebrote de infecciones invasivas neumocócicas que alcanzó el 40,9% de las IBI diagnosticadas. Tanto las ondas de incidencia provocadas por la pandemia como las que sufren las IBIs de forma espontánea, refuerzan la necesidad de diseñar sistemas sólidos de vigilancia de estas enfermedades.

Los artículos recogidos en esta tesis tienen sus limitaciones:

Primero, que el registro que sirve de base de la tesis, por su carácter unicéntrico, exige tener cautela a la hora de extrapolar los resultados. Sin embargo, pueden ser útiles en poblaciones de características similares.

Se trata de los siguientes artículos: “Characteristics of children with microbiologically confirmed invasive bacterial infections in the emergency department”; “Markers for invasive bacterial infections in previously healthy children”; “Repeated Emergency

Department Visits Among Children with Invasive Bacterial Infections"; "Impact of the COVID-19 pandemic on pediatric invasive bacterial infections".

Aunque el registro de pacientes se ha realizado de forma prospectiva, su análisis ha sido retrospectivo, lo que puede haber ocasionado alguna pérdida de datos. Su fortaleza viene condicionada por provenir del historial electrónico del servicio pediátrico de urgencias, basado en la base de datos electrónica habilitada por el sistema público de salud. El tamaño de la muestra investigada siempre puede ser mayor, pero es una muestra que ha ido aumentando año tras año y el registro aún sigue abierto. Los pacientes en los que no se aislaron bacterias en sangre o líquido cefalorraquídeo no se incluyeron en la investigación, por lo que no se ha podido determinar la especificidad y los valores predictivos de los diferentes análisis sanguíneos, pero es especialmente relevante conocer su sensibilidad en el momento de atender a estos pacientes.

Segundo, las limitaciones que presenta el artículo con registro unicéntrico ("Prevalence of Occult Bacteremia in Infants With Very High Fever Without a Source") que tiene como objetivo calcular la prevalencia de la bacteriemia son similares al anterior, pero al tratarse de datos que se han recogido prospectivamente, es poco probable que se haya perdido algún paciente. En el caso del multicéntrico ("Occult bacteremia in young children with very high fever without a source: a multicenter study"), la limitación principal es el tamaño muestral. Es cierto que el objetivo inicial era recoger entre 500 y 1.000 pacientes, pero cuando la investigación llegó a 200 y la tasa de bacteriemia era del 3%, preferimos publicar los resultados. No nos pareció ético continuar con la investigación sin comunicar por su trascendencia los resultados logrados hasta ese momento y así lo aprobó la revista científica.

Tercero, nuestro registro no fue diseñado para determinar la gravedad o caracterización del estreptococo del grupo B o del *E. coli*, pero los datos y resultados recogidos dan valor a las conclusiones obtenidas ("Paediatric Escherichia coli bacteraemia presentations and high-risk factors in the emergency department"; "Late-onset Group B Streptococcus Bacteremia Evaluated in the Pediatric Emergency Department and Risk Factors for Severe Infection"). Es cierto que en un artículo hemos analizado en gran medida las infecciones urinarias invasivas por *E. coli*, aunque sabemos que no es el único microorganismo causante de infecciones urinarias. Por tanto, los resultados no pueden extenderse a todas las infecciones urinarias invasivas y, además, analizamos también bacteriemias provocadas por *E. Coli* sin infección urinaria. En lo que se refiere al estudio del LCR, aunque quizá sean necesarias más y mayores investigaciones, nuestros datos apoyan la recomendación de la realización de la punción lumbar en niños menores de dos meses afectados de bacteriemia por *E. coli*.

Finalmente, en el subanálisis del estudio del estreptococo del grupo B no se tuvieron en cuenta todos los factores de riesgo. Los criterios de ingreso de los pacientes en la UCI quizá no fueron homogéneos o incluso los criterios para iniciar el soporte respiratorio hemodinámico. Sin embargo, creemos que los datos recopilados nos permiten realizar una caracterización de las bacteriemias producidas por el estreptococo del grupo B. Es más, nuestra investigación (los factores de riesgo estuvieron presentes en menos del 20% de las bacteriemias tardías producidas por estreptococo del grupo B) refuerza la idea de que la antibioterapia intraparto tiene más impacto sobre la bacteriemia precoz y menos frente a la tardía, y que exige la valoración de instaurar otras medidas, como las vacunas multivalentes que se implantarán en un futuro en mujeres embarazadas.

CONCLUSIONES

Este trabajo de investigación puede contribuir al conocimiento de las características clínicas que una IBI puede presentar en un servicio de urgencias pediátrico de nuestro entorno, tras los diferentes cambios sanitarios y sociales que se han producido en los últimos años. Por otro lado, puede ser una herramienta para aumentar el conocimiento de la gama de recursos con los que contamos para identificarlas.

Conclusiones por objetivos respectivamente.

- **Caracterizar la presentación clínica de las IBI confirmadas y describir la gravedad de las IBI en pacientes menores de catorce años.**

Characteristics of children with microbiologically confirmed invasive bacterial infections in the emergency department. EJEM 2018.

  - La edad del paciente y la bacteria patógena aislada tienen un gran peso en la caracterización de las IBI pediátricas actuales. Los pacientes más jóvenes previamente sanos son los que más las padecen.
  - La evolución del paciente con IBI en general es buena. Se relacionan con procesos más graves los pacientes que no llegan estables al servicio de urgencias, los que tienen algún otro síntoma asociado además de la fiebre y la corta duración del proceso.
  - *S. pneumoniae* ha sido el responsable de la mayor parte de las muertes y secuelas graves, seguido por *N. meningitidis*.

Repeated Emergency Department Visits Among Children with Invasive Bacterial Infections. PIDJ 2021.

  - No identificar adecuadamente a los pacientes con IBI en la primera consulta atendida en un servicio de urgencias y la no administración de

antibioterapia está relacionado con un peor pronóstico. Se deben diseñar herramientas más adecuadas para la identificación temprana de las IBI.

- **Analizar el valor de los test sanguíneos habituales (recuento leucocitario, número absoluto de neutrófilos, proteína C reactiva y procalcitonina) que se realizan para la identificación de IBI en pacientes menores de catorce años.**

Markers for invasive bacterial infections in previously healthy children. Am J Emerg Med. 2021.

  - Los pacientes con IBI presentan alteraciones de los marcadores sanguíneos más frecuentemente utilizados en un servicio de urgencias. La sensibilidad de estos marcadores varía en función de la bacteria causante y del diagnóstico final.

- **Evaluar la indicación de los test en sangre, en el manejo de niños de 3 a 24 meses de edad con fiebre sin focalidad y estabilidad clínica**.

Prevalence of Occult Bacteremia in Infants With Very High Fever Without a Source. PIDJ 2018.

  - La recomendación de no testar a lactantes febriles con buen estado general puede que deba ser reconsiderada en aquellos pacientes con fiebre sin foco $\geq$ 40,5ºC.

Occult Bacteremia in Young Children with Very High Fever Without a Source: A Multicenter Study. PIDJ 2020.

  - Aunque no existen recomendaciones para el cribado sistemático de bacteriemia oculta en lactantes entre 3 a 24 meses de edad con fiebre

sin foco y buen estado general, es probable que sea necesaria una revisión de estas recomendaciones cuando la temperatura sea igual o superior a 40,5ºC, independientemente del estado de vacunación.

- **Describir la presentación clínica de las infecciones invasivas de *E. coli* e investigar posibles perfiles y su posible relación con la gravedad.**

Paediatric *Escherichia coli* bacteraemia presentations and high-risk factors in the emergency department. Acta Paediatr 2021.

  - La bacteriemia provocada por *E. coli* atendida en un servicio pediátrico de urgencias, tiene cuatro tipos de presentación y la gravedad de cada una de ellas es diferente. La bacteriemia asociada a la infección urinaria fue la más frecuente en pacientes menores de 12 meses que estaban estables y se relacionó con buena evolución. La evolución de los más mayores, los que no llegaron estables y los que no eran previamente sanos fue peor. Es inusual que pacientes de más de dos meses sufran una meningitis provocada por *E. coli*.

- **Describir la presentación clínica de la infección invasiva del estreptococo del grupo B e investigar su posible relación con su gravedad.**

Late-onset Group B *Streptococcus* Bacteremia Evaluated in the Pediatric Emergency Department and Risk Factors for Severe Infection. PIDJ 2022

  - Los niños con bacteriemia tardía derivada del estreptococo del grupo B desarrollan con frecuencia sepsis y meningitis; la tasa de mortalidad y morbilidad no son despreciables, sobre todo en aquellos que el

triángulo de evaluación identifica como inestables y presentan leucopenia. Son precisas nuevas estrategias de prevención.

- **Objetivos secundarios: describir el impacto de una pandemia no esperada en la epidemiología de las IBI que se han identificado en un servicio de urgencias pediátrico.**

Impact of the COVID-19 pandemic on pediatric invasive bacterial infections. An Pediatr (Engl Ed). 2023.

  - En relación con los cambios en la prevalencia de IBI durante la pandemia, es necesario diseñar sistemas de vigilancia sólidos que controlen la evolución de las mismas, para que los profesionales que integran el sistema sanitario estén preparados para afrontar una nueva situación similar.

FUTURO

¿Y en el futuro qué? Es un gran reto. La historia nos ha enseñado en tantas ocasiones la importancia de la investigación. En un mundo que ha cambiado tanto en las últimas décadas, la investigación es absolutamente necesaria para entender hasta qué punto los cambios sociales influyen en la decisión de una familia de llevar o no a su niño al servicio de urgencias; para entender el impacto que tiene sobre el médico y el sistema de salud conocer de forma más precisa el riesgo de IBI que tiene el paciente al que se enfrenta; o, por qué no, con la ayuda de las nuevas tecnologías, para conocer las herramientas que nos faciliten la identificación de una IBI en el niño que es atendido en un servicio de urgencias.

Aunque las claves podrían ser visibles en muchos campos, yo mencionaría cuatro en esta tesis.

- Las medidas de prevención son imprescindibles. La implantación de programas de vacunación tal y como se habló en la discusión y como se vivió y quedó demostrado sobre todo durante la pandemia marca un hito. El consejo asesor de Vacunas de la Asociación Española de Pediatría tiene recomendaciones claras sobre la prevención de la enfermedad neumocócica y meningocócica invasiva. Existen muchas expectativas puestas en las diferentes vacunas conjugadas multivalentes que se comercializarán en un futuro cercano, así como la vacuna contra el estreptococo del grupo B propuesto en mujeres embarazadas.
- Nuevas técnicas que faciliten y aceleren la identificación de enfermedades infecciosas. Los sistemas de cultivo anteriores se combinan actualmente con nuevas técnicas. En los últimos años se han dado diversos avances dentro de las técnicas de identificación, entre las que se encuentran las que se basan en la PCR.

La técnica estándar se basa en la amplificación del material genético (ADN o ARN); genera una gran cantidad de copias que posteriormente se contabilizan por inmunofluorescencia[217]. Esta técnica permite diagnosticar numerosos procesos patológicos y se realiza actualmente en sangre, líquido cefalorraquídeo, líquido pleural, secreciones de las vías respiratorias, etc. Las nuevas técnicas han permitido reducir varios pasos y tener resultados en muy poco tiempo. No obstante, se recomienda que estas técnicas se realicen en pacientes seleccionados, dentro de abordajes diagnósticos específicos, como el resto de pruebas complementarias, con el fin de evitar falsos positivos y tratamientos y acciones innecesarias.

- Tratamientos. El aumento de las resistencias a los antibióticos es la principal fuente de preocupación. Restricciones en el espectro antibiótico, indicaciones adecuadas, ... serán imprescindibles para el control de las IBIs si queremos tener disponibles una batería de antibióticos eficaces.
- La pandemia, pero también la situación prepandémica, ha demostrado cómo son imprescindibles unos sistemas sólidos que controlen y monitoricen la evolución de las enfermedades infecciosas. Estos, además de realizar la monitorización de las IBIs y otras enfermedades, facilitan la toma de decisiones y la realización de acciones puntuales o más generales.

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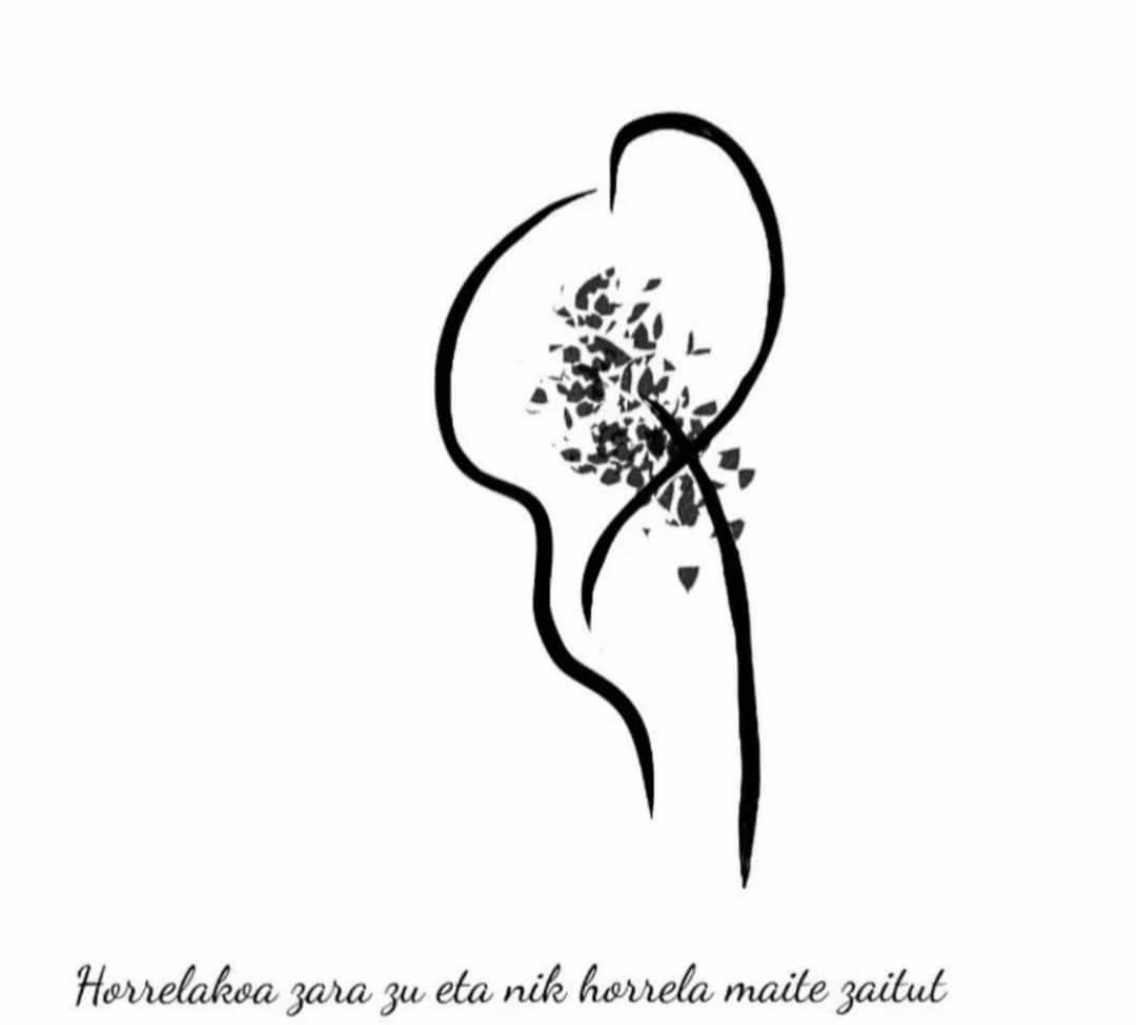
HITZATZEA

Oso presente…



Zure bidearen azken hilabeteak nire tesiaren azken hilabeteen parean joan ziren garaian, txarrenari onena zelan atera irakatsi zenigulako, utzi diguzun ondarea zainduko dogulako.

Amets, amets egin…

Todas las horas que quedan, van a pasar; es inevitable (Izaro)

TESI HONETAN, IKERKUNTZAN, BIZITZAN… ARGI IZAN
PASIOA DELA EXIGITZEA ZILEGI DEN GUTXIENEKOA
eta
DENBORA BAINO EZ POLIGRAFO BAKARRA (Btx).

CARPE NOCTEM (BTx)