REVIEW

Bacterial pathogens causing neonatal sepsis in Peru: a systematic review

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ABSTRACT

Neonatal sepsis is a significant cause of mortality worldwide, with a heterogeneous clinical presentation that makes early diagnosis difficult. In Peru, it represents the leading cause of death in infants under one year of age, with coagulase-negative *Staphylococcus* being identified as the most frequent causal pathogen. However, microbiological characterization and analysis of bacterial resistance in the Peruvian neonatal population is still limited. The objective was to determine the microbial characteristics and resistance profile of microorganisms causing neonatal sepsis in Peru. The study followed the PRISMA Guidelines, and the protocol was registered in PROSPERO (International Prospective Register of Systematic Reviews; CRD42024506552). PubMed/MEDLINE, LILACS, SciELO, Scopus, and Web of Science were searched systematically from their inception until February 16, 2024. Quality was assessed using the Agency for Healthcare Research and Quality (AHRQ) checklist for cross-sectional studies and the Newcastle-Ottawa scale for cohort studies. Of the 647 studies identified, 15 were selected for a complete evaluation. Six studies were included in the final analysis, covering 2016 to 2022. Two articles were considered of good quality and four of medium quality. In five studies, *Staphylococcus* coagulase negative was the most frequently isolated bacterium. Extended-spectrum beta-lactamase (ESBL)--producing bacteria were reported in 4 of the six studies, ranging from 8.2 to 83.1 %. The combination of ampicillin with some was the most frequently used as the first line. The reports revealed that coagulase-negative *Staphylococcus* was the most frequent causative agent in neonatal sepsis. The most frequent resistance pattern isolated was ESBL production, and the first line of antimicrobial therapy was ampicillin in combination with some aminoglycoside.

Keywords: Neonatal Sepsis; Antibiotic Resistance; *Staphylococcus*; Bacteria/pathogenicity (Source: MeSH)

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Patógenos bacterianos causantes de sepsis neonatal en Perú: una revisión sistemática

RESUMEN

La sepsis neonatal es una importante causa de mortalidad a nivel mundial, con una presentación clínica heterogénea que dificulta su diagnóstico temprano. En Perú, representa la principal causa de muerte en lactantes menores de un año, siendo *Staphylococcus* coagulasa negativo identificada como el patógeno causal más frecuente. Sin embargo, la caracterización microbiológica y el análisis de resistencia bacteriana en la población neonatal peruana aún es limitada. El objetivo fue determinar las características microbiológicas y el perfil de resistencia de los microorganismos causantes de sepsis neonatal en Perú. El estudio se llevó a cabo siguiendo las directrices PRISMA y el protocolo fue registrado en PROSPERO (International prospective register of systematic reviews; CRD42024506552). Se realizó la búsqueda en "PubMed/MEDLINE", "LILACS", "SciELO", "Scopus" y "Web of Science", de manera sistemática, desde su inicio hasta el 16 de febrero del 2024. Se evaluó la calidad mediante la lista de verificación de la Agencia para la Investigación y Calidad de la Atención Médica (AHRQ) para estudios transversales y la escala Newcastle-Ottawa para estudios de cohortes. De 647 estudios identificados, 15 se seleccionaron para evaluación completa. Se incluyeron seis estudios en el análisis final, abarcando un período desde 2016 hasta 2022. Se consideraron dos artículos de buena calidad y cuatro de mediana calidad. En cinco de los seis estudios *Staphylococcus* coagulasa negativo fue la bacteria más frecuentemente aislada. Las bacterias productoras de betalactamasas de espectro extendido (BLEE) fueron reportadas en 4 de los 6 estudios en un rango de 8.2 a 83.1 %. La combinación de ampicilina con algún aminoglucósido fueron los más frecuentemente usados como primera línea. Los reportes considerados revelaron que el agente causal más frecuente en la sepsis neonatal fue *Staphylococcus* coagulasa negativo. El patrón de resistencia más frecuente aislado fue la producción de BLEE y la terapia antimicrobiana de primera línea fue ampicilina en combinación con algún aminoglucósido.

Palabras clave: Sepsis Neonatal; Resistencia a Antibióticos; *Staphylococcus*; Bacterias/patogenicidad (Fuente: DeCS)

INTRODUCTION

Neonatal sepsis is considered one of the leading causes of mortality worldwide. Its clinical presentation is heterogeneous and non-specific, representing a challenge for early and timely diagnosis. Confirmation of sepsis requires the isolation of a microorganism from blood cultures or sterile fluids. (1) Depending on the time of onset, it can be classified into early onset (when it occurs within the first 72 hours of life) and late-onset (after 72 hours of life). This classification is also helpful in determining the pathogen responsible (2).

In Peru, neonatal sepsis is the leading cause of death among infants under one year of age (66.6 %). It is also the second leading cause of death in neonates (21.77 %), surpassed only by conditions associated with prematurity (3). A study at the Instituto Nacional Materno Perinatal in Lima, Peru, identified coagulase-negative *Staphylococcus* as the most frequent causative agent of neonatal sepsis. Of the 489 subjects analyzed, it was found that the rates of multidrug-resistant microorganisms reached approximately 80 % (4). However, the information available on microbiological characterization and antimicrobial resistance in the Peruvian pediatric population is still limited. Therefore, this systematic review aimed to determine the microbial characteristics of bacteria isolated in neonates with a definitive diagnosis of sepsis. Likewise, the resistance profile to different antibiotics of the isolated bacteria was characterized.

MATERIALS AND METHODS

The present work was conducted and reported according to the Preferred Reporting Guidelines for Systematic Reviews and Meta-Analyses (PRISMA). Our protocol has been previously registered in PROSPERO (International Prospective Register of Systematic Reviews; CRD42024506552) and is available in full at https://www.crd.york.ac.uk/prospero/.

Search strategy

The databases "PubMed/MEDLINE", "LILACS", "SciELO", "Scopus" and "Web of Science" were systematically searched from their inception until February 16, 2024, by two independent researchers (authors SO and SB). The search used appropriate keywords or MeSH terms (supplementary material). The search was conducted, including articles published in English and Spanish. For potentially eligible articles, the investigators also checked references of relevant reviews and retrieved articles. When possible, to obtain missing data, the investigators contacted the corresponding authors of potentially eligible articles.

Inclusion and exclusion criteria

The inclusion criteria were established as follows.

1. Studies between 2014 and 2024 were considered for inclusion.
2. The studies had to include neonatal patients (0 to 28 days) with a diagnosis of sepsis, confirmed by a positive blood culture result.
3. The studies had to provide detailed microbiological information on the etiological agent, including its resistance profile.

Exclusion criteria were established as follows

1. Commentaries, editorials, reviews, study protocols, and letters to the editor.
2. Studies without a confirmed diagnosis of sepsis by blood culture.
3. Non-peer-reviewed studies published as preprints.
4. Studies with incomplete data.

Data extraction

Titles and abstracts were independently reviewed by two investigators (AG and SO) to exclude duplicate studies; also, studies that did not meet the eligibility criteria mentioned above were excluded. Subsequently, the full text of potentially eligible studies was evaluated by two investigators (AG and SO). Discussions with a third investigator (SB) resolved any discrepancies between the reviewers. Finally, the selected studies were thoroughly reviewed, and data extraction was performed. The following data were extracted for further evaluation: year of publication, type of study, population, duration of hospitalization, duration of stay in the neonatal intensive care unit (NICU), sex, bacteria isolated by blood culture, resistance profile, duration of treatment, type of sepsis and mortality rate.

Studies' quality evaluation

The quality of the included articles was assessed using the 11-item checklist recommended by the Agency for Healthcare Research and Quality (AHRQ) for cross-sectional studies (https://www.ncbi.nlm.nih.gov/books/NBK35156/). (5) the Newcastle-Ottawa Scale (NOS) tool was used for the only included cohort study. By applying eight questions, three parameters were evaluated: selection criteria, comparison criteria, and outcomes. For the AHRQ, a score of "1" was assigned to an item only if the answer was "Yes" and "0" when the answer was "No" or "Unclear". Study quality was assessed as "low quality" (score of 0-3), "moderate quality" (score of 4-7), and "high quality" (score of 8-11). For the NOS evaluation, one or two stars were assigned to each question in each domain according to a favorable assessment; if the review was negative or without information, no star was assigned. Sound quality: 3 or 4 stars in the selection domain, 1 or 2 stars in the comparability domain, and 2 or 3 stars in the outcome/exposure domain. Acceptable quality was considered as two stars in the selection domain, 1 or 2 stars in the comparability domain, and 2 or 3 stars in the outcome/exposure domain. Low quality was considered as 0 or 1 star in the selection domain, 0 stars in the comparability domain, or 0 or 1 stars in the outcome/exposure domain. (6) The third investigator also resolved Any discrepancies in the assessment when necessary (SB).

RESULTS

Articles selection

Our search identified 647 studies from January 2014 to January 2024. After removing duplicates (100), we proceeded to screen the remaining 547 studies by titles and abstracts. Fifteen studies were selected for full-text evaluation. Six studies were selected for this review after eliminating studies that did not contain specific information about the Peruvian population or microbiological characteristics (Figure 1).

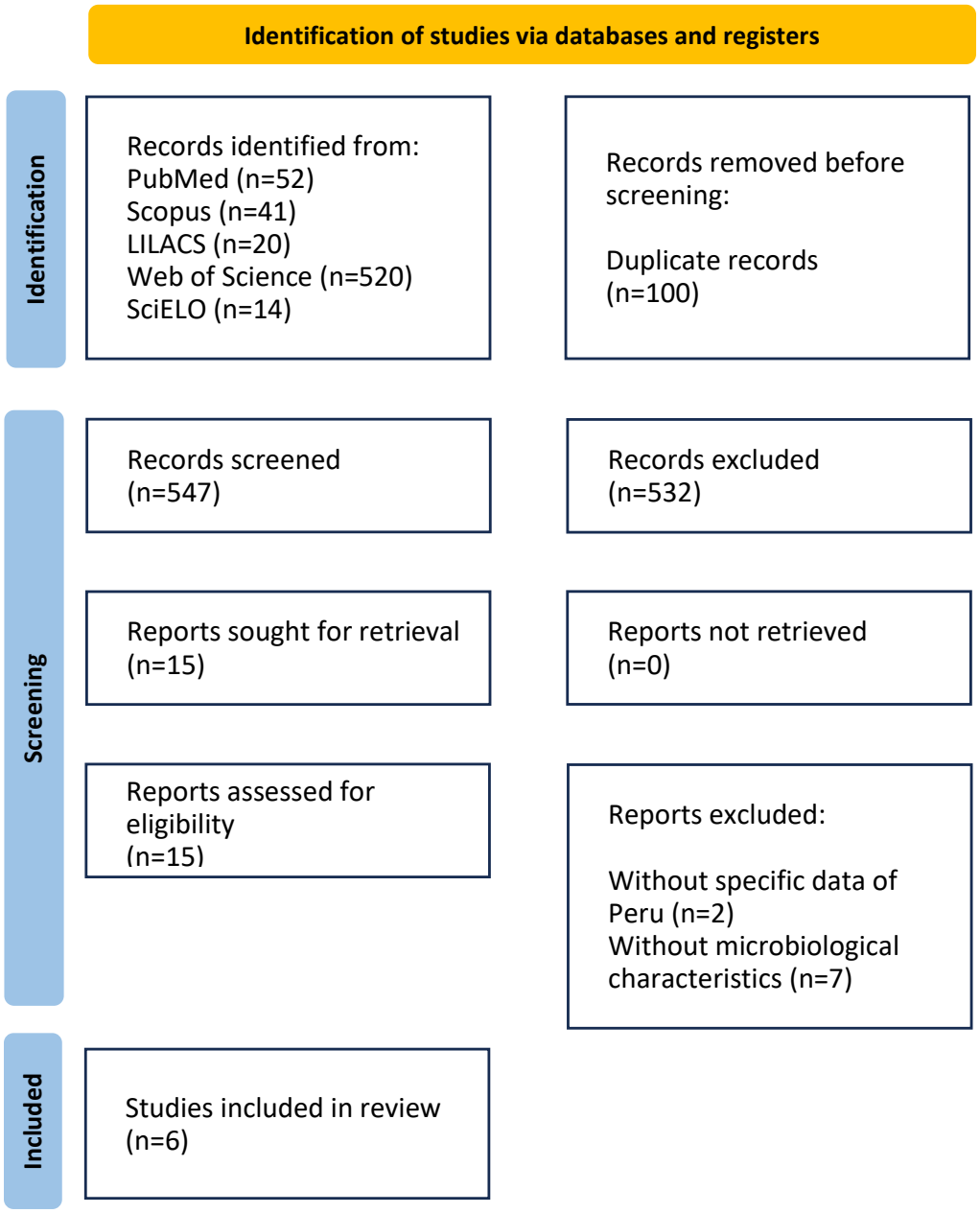

Figure 1. PRISMA flow chart and description of the study selection process.

General characteristics of the articles

The oldest studies were collected in 2016 by Alvarado-Gamarra *et al.* (7), while the most recent was from 2022 by Vizcarra-Jimenez *et al.* (8). Five cross-sectional studies and one retrospective cohort study were included. The largest population studied was 489 neonates, while the smallest included 200 neonates. Four articles considered the sex variable for their studies, and three reported a predominance of male neonates. Only two studies considered admission to the Neonatal Intensive Care Unit (NICU), 7 and 13 days stay in that service. Three studies only included the diagnosis of late-onset sepsis. Only one study found early-onset sepsis more frequent than late-onset sepsis (Table 1).

Table 1. Characteristics of the selected studies

Author, year	Type of study	Sample	Duration of hospitalization	Time in NICU	Sex	Bacteria isolated	Resistance patterns	Duration of treatment	Type of sepsis	Mortality rate
Vizcarra-Jiménez *et al.*, (8) 2022	Retrospective cohort	n=288	7(6-14)**	7(5-13)**	Masculine n=145 Femenine n=143	*Klebsiella pneumoniae* n=16 *Staphylococcus* n=5 *Escherichia coli* n=3 *Enterobacter cloacae* n=2	ESBL n=19	NI	EOS n=223 LOS n=61	180 per 1000 neonates
Ruiz B. *et al.*, (9) 2022	Cross-sectional	n=303	NI	NI	Masculine n=173 Femenine n=130	*Staphylococcus* n=15 *Staphylococcus aureus* n=2 *Listeria monocytogenes* n=1 *Enterococcus faecalis* n=1 *Burkholderia gladioli* n=1	*Staphylococcus* coagulase positive resistant to clindamicin n=11, oxacillin n=13, ampicillin n=1, cefotaxime n=1, gentamicin n=4	NI	LOS n=303	NI
Herbozo *et al.*, (3) 2021	Cross-sectional	n=234	NI	NI	NI	*Staphylococcus* n=89 *Klebsiella Pneumoniae* n=5 *Staphylococcus aureus* n=16 *Pseudomonas* spp. n=14 *Escherichia coli* n=14 *Enterobacter* spp. n=11 *Candida* spp. n=11 *Serratia* spp. n=10 *Enterococcus* spp. n=5 *Stenotrophomonas* spp. n=4 *Proteus* spp. n=3 *Acinetobacter* spp. n=2 *Streptococcus agalactiae* n=2 *Citrobacter* spp. n=1 *Listeria monocytogenes* n=1	ESBLn=19	NI	LOS n=234	197(7.2 %)

Author, year	Type of study	Sample	Duration of hospitalization	Time in NICU	Sex	Bacteria isolated	Resistance patterns	Duration of treatment	Type of sepsis	Mortality rate
Quispe *et al.*, (4) 2020	Cross-sectional	n=489	NI	NI	Masculine n=206 Femenine n=283	*Staphylococcus* n=466 *Acinetobacter* spp. n=48 *Klebsiella* spp. n=42 *Staphylococcus aureus* n=15 *Escherichia coli* n=30 *Staphylococcus* spp. n=35 *Enterococcus* spp. n=13 *Serratia* spp. n=12 *S. maltophilia* n=7 *Pseudomona aeruginosa* n=2 *Enterobacter* spp. n=1	MDR n=389 ESBL=64 Presence of carbapemenases =13	NI	LOS n=340 EOS n=149	NI
Rueda *et al.*, (10) 2019	Cross-sectional	n=408	29(18-46)**	13(5-26)**	NI	*Staphylococcus* n=17 *Staphylococcus aureus* n=3 *Enterococcus* spp. n=3 *Klebsiella* spp. n=7 *Escherichia coli* n=6 *Enterobacter* spp. n=3 *Pseudomona aeruginosa* n=2 *Acinetobacter iwoffi* n=1 *Empedobacter brevis* n=1	MRSA n=3 Cefalosporines n=12 Vancomicine n=2 Carbapenems n=4	11.04 ± 7.57* (<1500g) 9.52 ± 5.52* (>1500g)	LOS n=408(100)	NI
Alvarado-Gamarra *et al.*, (7) 2016	Cross-sectional	n=200	30(15,5-55,5)**	NI	Masculine n=111 Femenine n=89	*Staphylococcus* n=10 *Staphylococcus* aureus n=6 *Klebsiella* spp. n=4 *Escherichia coli* n=3 *Pseudomona aeruginosa* n=1 *Enterococcus* spp. n=1 *Streptococcus viridans* n=1	MRSA n=4 ESBLn=6 Staphylococcus oxacillin resistant n=9	14.5(10-21)**	LOS n=10 EOS n=16	0.97 per 1000 neonates

***NI**: No information, **ESBL**: Extended Spectrum Betalactamases, **MDR**: Multidrug resistant, **MRSA**: Methicillin-resistant Staphylococcus aureus, **NICU**: Neonatal intensive care unit, **EOS**: Early-onset sepsis, **LOS**: Late-onset sepsis.*
Mean ± Standard Deviation, ** Median (IQR**)*

Quality of the included studies

Only one cohort study was included for which the NOS quality assessment tool was used, and there was no discrepancy among the reviewers. The highest score was achieved for the selection and outcome criteria (4 and 3 stars, respectively). The final sum of the three parameters showed the article to be of good quality (Table 2). The AHRQ tool was used to analyze the observational studies. Of the five studies included, only 1 scored 8, classifying it as high quality. Alvarado-Gamarra's study had the lowest score; however, it still achieved a moderate quality grade. No studies of low quality were reported. None of the studies presented evidence that the people included in their studies were a significant sample of the population (P3) (Table 3).

Table 2. Examination of quality risk with the NOS tool of the included studies

Study	Examinators	Selection	Comparative	Result	
Vizcarra-Jiménez *et al.*, (8) 2022	R1	4*	1*	3*	Good quality
	R2	4*	1*	3*	

Table 3. Examination of quality risk with the AHRQ tool of included studies

Studies	Reviewers	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	Total	Result
Ruiz B. *et al.*, (9) 2022	R1	✓	✓	x	✓	✓	✓	✓	✓	✓	x	✓	8	High
	R2	?	✓	x	✓	✓	✓	✓	✓	✓	x	✓		
	CR	?												
Herbozo *et al.*, (3) 2021	R1	?	✓	x	✓	?	✓	x	✓	✓	x	✓	6	Moderate
	R2	?	✓	x	✓	✓	✓	x	✓	✓	x	✓		
	CR					?								
Quispe *et al.*, (4) 2020	R1	?	✓	x	✓	✓	✓	x	✓	✓	x	✓	7	Moderate
	R2	?	✓	x	✓	✓	✓	x	✓	✓	x	✓		
Rueda *et al.*, (10) 2019	R1	?	✓	x	✓	✓	✓	x	✓	✓	x	✓	7	Moderate
	R2	?	✓	x	✓	✓	✓	x	✓	✓	x	✓		
Alvarado-Gamarra *et al.*, (7) 2016	R1	?	?	x	✓	✓	✓	x	✓	?	?	✓	4	Moderate
	R2	?	?	x	✓	✓	✓	x	✓	?	?	x		
	CR											x		

***Green box**: yes* ***Green red** : no* ***Green yellow**: unclear*

Microbiological profile of patients with sepsis

In five of the six studies, coagulase-negative *Staphylococcus* was the most frequently isolated bacterium. Only one study reported a predominance of Klebsiella pneumoniae species. *Escherichia coli* was reported in 5 of the six studies analyzed. Other gram-negative bacilli reported were *Pseudomonas* spp. in 4 of the six studies and Enterobacter spp. in 3 of 6. Other gram-positive bacilli found were *Enterococcus* spp. and Listeria monocytogenes; however, they were reported in lower percentages (Table 1). All the articles included reported a resistance profile. Bacteria with extended-spectrum beta-lactamases (ESBL) were reported in 4 of the six studies, ranging from 8.2 to 83.1 %. Methicillin resistance in *Staphylococcus* aureus was reported in 2 articles, including one in which all three isolates had this resistance profile. Only one study reported a multidrug-resistant profile, with 79.6 % of the samples obtained. Two studies reported the antibacterial resistance of coagulase-negative Staphylococcus, with the highest resistance values to Oxacillin (Table 1).

Antimicrobial Treatment and Other Therapies Used

Only one study reported no antimicrobial treatment. The combination of ampicillin with some aminoglycoside (Gentamicin or Amikacin) was the most frequently used as the first line. One study reported using fluconazole and amphotericin as part of first-line treatment. Another of the most commonly used combinations was Ampicillin/Cefotaxime. Only one study reported second-line treatments after failure of a first drug or combination. In this case, Vancomycin or the Vancomycin/Ceftazidime combination was used. The main reason for the decision to switch was the poor clinical progression of the patient (50 %). Secondly, blood culture results decided the switch. Two studies reported the use of additional treatments for the management of neonatal sepsis. The most commonly used additional treatment was mechanical ventilation. Another treatment reported by both studies was surfactant (Tabla 4).

Table 4. Characteristics of antibiotics and other treatments used

Author, year	First line	Second line	Motive of change	Other therapies used
Vizcarra-Jiménez *et al.*, (8) 2022	Oxacillin n=24 Ampicillin n=271 Aminoglucosidos n=265 Cefotaxime n=40 Ceftazidime n=15 Imipenem /meropenem n=65 Vancomycin n=71 Metronidazol n=8 Clindamycin n=2 Fluconazole n=4 Amphotericin n=3	NI	NI	Mechanical ventilation n=82 Vasopressors n=30 Surfactant n=44 Blood transfusion n=24 Phototherapy n=106 Corticosteroid n=9
Ruiz B. *et al.*, (9) 2022	Ampicilin /amikacin n=17 Ampicilin /cefotaxime n=3	NI	NI	NI
Herbozo *et al.*,(3) 2021	Vancomycin /Amikacin	NI	NI	NI
Quispe *et al.*, (4) 2020	/Amikacin n=127 Ampicillin n=115	NI	NI	NI

Author, year	First line	Second line	Motive of change	Other therapies used
Rueda *et al.*, (10) 2019	Vancomycin n=115 Imipenem n=73 Meropenem n=51 Ceftazidime n=42 Metronidazol n=22 Cefotaxime n=22 Ciprofloxacin n=17 Piperacillin /Tazobactam n=15 Cefepime n=12 Linezolid n=8	NI	NI	NI
Alvarado-Gamarra *et al.*, (7) 2016	Ampicillin /Amikacin n=10 Ampicillin /Cefotaxime n=6 Meropenem n=2 Vancomycin /Ceftazidime n=2 Amikacin n=1 Ciprofloxacin n=1 Ampicillin /Cefotaxime /Metronidazol n=1 Vancomycin n=1	Vancomycin n=6 Vancomycin /Ceftazidime n=3 Meropenem n=2 Ampicillin /Cefotaxime n=1 Meropenem /Amikacin n=1 Vancomycin /Ciprofloxacin n=1	Poor clinical course n=7 Blood culture result n=6 Both n=1	Mechanical ventilation n=11 Surfactant n=9 CPR n=10

***NI**: no information, **CPR**: cardiopulmonary resuscitation*

DISCUSSION

In this systematic review, we sought to describe the microbiological characteristics of bacteria isolated from patients diagnosed with neonatal sepsis in Peru. At the end of the review, six articles were included for evaluation. Bacteria belonging to the genus *Staphylococcus* were isolated most frequently, similar to other studies in which coagulase-negative *Staphylococcus* is reported as the most prevalent (11). Within the group of gram-negative bacteria, Klebsiella pneumoniae is considered the second or third most frequent cause (12). One of the studies presented a similar result since K. pneumoniae was isolated in 50.4 % of the patients with blood cultures. In previous reports, *E. coli* is considered among the primary etiologic agents in cases of neonatal sepsis (13). However, in our review, the frequency was lower than other bacteria. Two studies reported neonatal sepsis of fungal origin, giving amphotericin and fluconazole as treatment options. Although the report of fungal neonatal sepsis was not the objective, we consider it essential to point out the treatment used in some cases.

Antimicrobial resistance is a significant public health problem and is considered one of the greatest threats to health worldwide. The increase and emergence of resistant bacteria have also been reported in cases of neonatal sepsis. In our study, ESBL-producing isolates were found with high frequency, mainly in gram-negative isolates identified as K. pneumoniae and *E. coli*. Among enterobacterias, both K. pneumoniae and *E. coli* have the highest incidence of resistance, having multidrug-resistant (MDR) and ESBL-producing profiles and even other carbapenemases (14). Gram-positive bacteria have also increased in MDR phenotypes. Methicillin-resistant *Staphylococcus* aureus (MRSA) variants have been described in cases of neonatal sepsis worldwide (15). Our review identified a frequency of up to 100 % of neonatal MRSA sepsis in one of the included studies. The emergence of MDR variants is exacerbated by poor policies on antibiotic trade and management, mainly in developing countries (16, 17). There is a scarcity of reports and characterization of antimicrobial resistance in cases of neonatal sepsis in Peru, so the actual situation still needs to be discovered. Although the isolation and microbial characterization results are reported in each health center, many of these are not published as part of the scientific literature.

Regarding treatments and lines of antibiotics, the combination of ampicillin with aminoglycosides is usually used and most frequently reported in all the included studies (18). Other agents such as vancomycin, carbapenems, and quinolones are reserved for cases where bacteria with resistance profiles such as ESBL or MRSA are found (19). One study reported using second-line drugs, including vancomycin, ceftazidime, cefotaxime, meropenem, amikacin, or ciprofloxacin, with the decision being based on the MRSA rates they found.

The study has limitations. First, the studies we included may differ from the reality of neonatal sepsis in Peru. This is due to the limited information available and published in the scientific literature. Additionally, due to our selection criteria, we excluded studies that needed the necessary microbiological details, such as bacterial identification and resistance profile. Second, the selected studies have a moderate to high risk of selection bias due to the criteria used to include participants, leading to low generalizability of the results. The limitations identified by our study highlight the need to increase and improve epidemiological research on neonatal sepsis and promote its publication to share information available for the generation of evidence-based medicine.

The present review on the microbiological characteristics of neonatal sepsis cases in Peru identified *Staphylococcus* spp. as the most frequent causative bacterial agent, followed by K. pneumoniae and *Escherichia coli*. Additionally, the most frequent resistance pattern in gram-negative bacilli was the production of ESBL, and the most frequently used first-line antimicrobial therapy was ampicillin in combination with gentamicin or amikacin.

Authors' contribution

Conceptualization: AG; data collection, management and curation: AG, SOV, SB; data analysis: AG, SOV, SB; visualization: AG, SOV, SB; drafting of original version: AG, SOV, SB; interpretation of results: AG, SOV, SB; drafting and revision of final version: AG, SOV, SB.

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The present study was self-funded.

Ethical aspects

Does not apply. The present study was based on the compilation of publications that have information in the public domain; likewise, no confidential data that have not been published for purely academic purposes are presented.

Conflicts of interest

The authors have no conflicts of interest associated with the material presented in the manuscript.

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