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REVIEW ARTICLE

Efficacy of empiric antibiotic treatment of late-onset neonatal sepsis caused by *Enterobacteriaceae*: A systematic review

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Significance and Impact of the Study: Neonatal infections due multidrug-resistant enterobacteria are a major threat in paediatric units. In this review, we examine whether the World Health Organization's recommended treatment regime remains applicable for late-onset neonatal sepsis caused by *Enterobacteriaceae,* in the time of increased antimicrobial resistance.

Keywords
empiric antibiotic treatment, neonatal sepsis, antimicrobial resistance, *Enterobacteriaceae*, systematic review.

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Abstract

Neonatal sepsis is a serious condition, where an adequate empiric antibiotic treatment is crucial. The objective of this systematic review is to assess whether the World Health Organization's recommended treatment regime remains applicable for late-onset neonatal sepsis caused by *Enterobacteriaceae*, in the time of increased antimicrobial resistance. *PubMed* was searched for articles from 2009 to 2020. A total of 49 articles were eligible for inclusion. The review was carried out in accordance with PRISMA guidelines. For *Klebsiella* spp. 100, 68 and 63% of the studies found sensitivity to ampicillin, gentamicin and third-generation cephalosporin in <50% of the isolates. For *Escherichia coli*, the corresponding values were 88, 50 and 42% respectively, whilst for *Enterobacter* spp. 100, 70 and 94% of the studies found <50% sensitivity to these antibiotics. Overall, there is low sensitivity to all agents in the WHO's recommended empiric treatment regimes (WHO recommends ampicillin plus gentamicin as first-line treatment and third-generation cephalosporin as second-line treatment). A revised guideline for empiric antibiotic treatment of neonatal sepsis is urgently needed due to the increased threat of antimicrobial resistant *Enterobacteriaceae* causing neonatal sepsis.

Introduction

Neonatal sepsis is a serious condition in newborns and continues to be a leading cause of morbidity and mortality worldwide (WHO, 2016). The 4th Millennium Development Goal aims to reduce child mortality by half, and the 15-year report in 2015 showed a reduction from 33 deaths to 19 deaths per 1000 live births between 1990 and 2015 (UN, 2015). However, in 2018, two-and-a-half million deaths occurred in the first month of life, accounting for 47% of paediatric deaths under the age of 15 (UNICEF, 2019). This makes the neonatal period the most vulnerable period for children, with the infectious disease being one of the main threats and where sepsis counts for 15% of newborn deaths (UNICEF, 2019).

Neonatal sepsis is divided into early-onset sepsis (EOS) and late-onset sepsis (LOS). The definition of early and late-onset sepsis varies across studies, where some define early-onset as sepsis appearing in the first 7 days of life, whilst others limit it to the first 72 h of life. Early-onset sepsis is usually due to vertical transmission from mother to newborn, whilst late-onset sepsis presents with a horizontal transmission with infection from the community or nosocomial infection from a prolonged hospital stay (Edwards, 2019).

The highest number of neonatal deaths occur in low to middle-income countries (UNICEF, 2019). In said

countries, there is also a higher burden of antimicrobial resistance, principally to Gram-negative bacteria (WHO, 2016). With increased antimicrobial resistance the world is faced with a serious global threat where common antimicrobial treatments are no longer effective.

Neonatal sepsis has a non-specific presentation and a large array of clinical signs and symptoms, making it difficult to diagnose (Kruse *et al.* 2013).

This highlights the importance for an adequate empiric antibiotic treatment to be established as neonatal sepsis is highly preventable in its early stages (Roy *et al.* 2017). The World Health Organization's (WHO) Pocketbook of Hospital Care for Children recommends ampicillin plus gentamicin as first-line empiric treatment and third-generation cephalosporin as second-line treatment (Wakai *et al.* 1996). With the increase of extended-spectrum β-lactamases (ESBL) producing *Enterobacteriaceae* (WHO, 2016), there is a concern for the applicability of this guideline. ESBL-producing gram-negative bacteria carry the encoding genes on plasmids that easily transfer between the bacteria, and often show resistance to other antibiotics as well, including amikacin and gentamicin (Roy *et al.* 2017).

With the rise of multi-drug resistant Gram-negative bacteria and ESBL producing *Enterobacteriaceae*, the common empiric antibiotic treatment regime may no longer be effective for a large proportion of the world's most vulnerable neonates. The levels of antibiotic resistance in Gram-negative bacteria isolated from neonatal patients with sepsis were higher than those in Gram-positive bacteria (Wu *et al.* 2009; Pius *et al.* 2016). The unspecific presentation of neonatal sepsis suggests that an early and adequate treatment with antimicrobial drugs is crucial.

This review will investigate the effectiveness of the WHO's recommended antibiotic treatment regime, as stated in the WHO recommendations, by reviewing the sensitivity pattern of *Enterobacteriaceae* in late-onset sepsis in studies across low-, middle- and high-income countries.

Results and discussion

Search results

A total of 733 articles were retrieved, and after excluding duplicates, 730 abstracts and titles were screened. Of these, 159 articles were retrieved for full-text reviewing, with a total of 49 articles eligible for inclusion (Fig. 1).

Study characteristics

Table S1 includes detailed information about the included articles in this review, with information on study type, study period, study location, type of centre and inclusion criteria. Most studies were retro- or prospective. The most frequent study location was India, with 9 studies, followed by Nepal with eight studies. Ten studies were done in low-income countries, and 30 studies in middle-income countries (World Bank, 2020). Nine studies were done in high-income countries, with 7 in Europe (World Bank, 2020). A total of 36 studies were done in tertiary referral centres, university teaching centres and/or neonatal intensive care units. All studies were conducted after 1995. Many used positive blood culture as an inclusion criterion, however, there are also studies including different cultures taken from other sites such as cerebrospinal fluid and urine.

Isolated pathogens

Across the studies included in this review, the most commonly isolated pathogens included *Klebsiella* spp, *Enterobacter* spp and *Escherichia coli*. The size of the studies varied widely, as seen in Table S2. In total, 23,555 subjects were included. The type of subjects varied across studies, where some referred to a total of neonates diagnosed with sepsis, whilst others referred to pathogens from positive cultures. The smallest study included 24 isolates (Shakir *et al.* 2014); a prospective study was done on invasive neonatal infection caused by *Escherichia coli*. Guiral *et al.* only included 48 subjects, also studying the antimicrobial resistance of *Escherichia coli* strains causing neonatal sepsis (Guiral *et al.* 2012). The five studies with the most subjects included 50% of the total subjects of all included studies (Muller-Pebody *et al.* 2011; Labi *et al.* 2016; Lu *et al.* 2016; Cailes *et al.* 2018; Jajoo *et al.* 2018), two of them in the United Kingdom (Cailes *et al.* 2018; Jajoo *et al.* 2018) and the others in middle-income countries.

We found that 10 articles did not include the incidence of late-onset sepsis, but for those articles that did, more than half reported a higher incidence of late-onset sepsis, apart from two articles where a specific late-onset neonatal sepsis population was studied (Saleem *et al.* 2013; Lutsar *et al.* 2014). In the articles where pathogen incidence in late-onset sepsis was reported, 66% showed a higher incidence of *Klebsiella* spp compared to *Escherichia coli* and *Enterobacter*. However, the definition of late-onset sepsis varied across studies. Most defined late-onset sepsis as sepsis occurring after 72 h of life, whilst others made a distinction at 48 h.

Antimicrobial resistance

The resistance pattern of the three most frequent *Enterobacteriaceae* species isolated in patients with neonatal

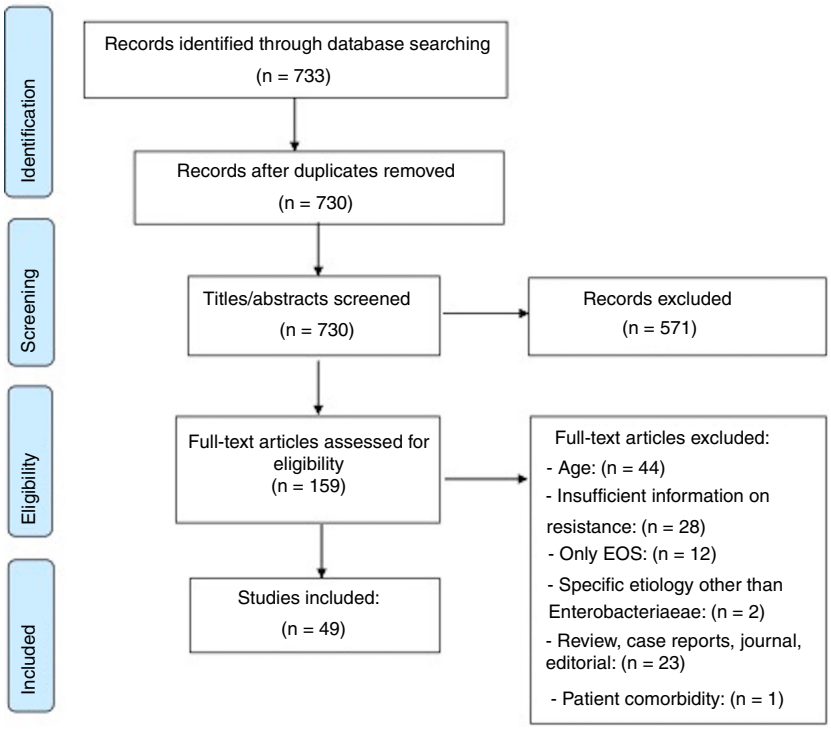

Figure 1 PRISMA flow diagram describing the process of selection of included articles. The vertical boxes on the left of the diagram indicate the stages of the systematic review process, according to the PRISMA statement regulations (PRISMA Statement, 2014).

sepsis (*Klebsiella* spp, *Enterobacter* spp, *Escherichia coli*) is presented in Tables 1–4. The selected studies employed standard methods for assessing antimicrobial resistance.

For *Klebsiella* spp, 23 of 25 studies that tested for ampicillin sensitivity showed sensitivity in <50% of the tested isolates (Table 1). Furthermore, 13 of the 25 studies showed total resistance to ampicillin where none of the tested isolates was sensitive. Gentamicin sensitivity was low across the studies, and more frequently tested. Thirty-five studies tested for gentamicin sensitivity in *Klebsiella* spp, and 23/35 studies showed sensitivity in <50% of tested isolates; however, only two studies had no sensitive isolates. Cefotaxime and Ceftriaxone were the most frequent third-generation cephalosporins studied, and 22 of the 36 studies testing for sensitivity showed <50% of sensitive isolates. In most cases, there was a correlation between third-generation cephalosporin resistance and resistance to either ampicillin and/or gentamicin (Table 1).

For *Escherichia coli,* 27 studies tested for sensitivity to ampicillin, with 23 of them with showing the sensitivity of <50% of the isolates, including 4 studies with no sensitive isolates (Table 2). However, these studies only included a small test size (<10 isolates tested). In total, 35 studies tested for gentamicin sensitivity, and we found 17 studies with <50% sensitive isolates of the total tested; 2 of them with no sensitive isolates, corresponding to the same small studies with total resistance to ampicillin. For third-generation cephalosporins, 14 of 34 studies showed <50% of tested isolates to be sensitive; 4 of them were without any sensitive isolates.

Lastly, for *Enterobacter,* all 10 studies investigating ampicillin sensitivity found <50% sensitive isolates. For gentamicin, 14 out of 20 studies had <50% sensitive isolates, and for third-generation cephalosporins, 16 out of 17 studies found <50% sensitive isolates (Table 3).

Sensitivity testing of *Enterobacteriaceae* spp collectively was carried out in 5 studies. Lutsar *et al.* (2014) tested for ampicillin, gentamicin and cefotaxime sensitivity, where only 1 isolate out of 21 tested was sensitive to ampicillin, but more than 50% of the tested *Enterobacteriaceae* were sensitive to gentamicin and cefotaxime (Table 4). Gyawali and Sanjana (2013), found <50% sensitivity to both ampicillin, gentamicin and cefotaxime. In contrast, Muller-Pebody *et al.* (2011) tested *Enterobacteriaceae* where all were more than 50% sensitive to cefotaxime monotherapy, and the combination therapies of amoxicillin plus cefotaxime and amoxicillin plus gentamicin. Vergnano *et al.* (2011) also produced results that showed more than 50% of the *Enterobacteriaceae* to be sensitive to amoxicillin plus cefotaxime and flucloxacillin plus gentamicin. Labi *et al.* (2016) showed 50% sensitivity to the combination ampicillin plus cefotaxime, but only 30%

Table 1 Sensitivity pattern of *Klebsiella* spp to empiric treatment. The columns are arranged by type of antibiotic, represented in an *x/y* format, where '*x*' represents the number of sensitive isolates and '*y*' represents the total number of isolates tested for the particular antibiotic. In some cases, included studies used alternative treatments or a combination of antibiotics, which are indicated in the right-most column. The identity of the therapeutic regimen in this column are indicated by superscript numbers, explained in the footnotes of the table

	AMP	GEN	CTX	CRO	Alternative treatments/ Combination therapy
Adhikari *et al*. (2014)	–	3/4	3/4	–	–
Anderson *et al*. (2013)	0/9	7/9	–	6/9	–
Bandyopadhyay *et al*. (2018)	–	–	38/57	38/57	–
Cailes *et al*. (2018)	–	–	–	–	123/134[5] 21/137[6]
Chandel *et al*. (2011)	2/113	57/113	66/113	–	–
Datta *et al*. (2014)	–	13/68	6/68	–	–
Gkentzi *et al*. (2018)	–	44/80	53/80	–	–
Jajoo *et al*. (2018)	–	8/50	8/50	8/50	–
Jiang *et al*. (2016)	–	13/17	0/13	–	–
Kabwe *et al*. (2016)	1/69	3/73	3/74	–	–
Kamath *et al*. (2010)	14/36	6/36	–	–	–
Kangozhinova *et al*. (2013)	–	2/12	–	1/12	–
Khassawneh *et al*. (2009)	0/27	8/29	–	–	10/23[3]
Kruse *et al*. (2013)	0/78	12/78	11/78	–	–
Labi *et al*. (2016)	–	–	–	–	–
Li *et al*. (2019)	0/15	25/31	2/29	1/13	–
Lu *et al*. (2016)	11/102	75/102	35/102	–	–
Marando *et al*. (2018)	0/26	4/26	5/26	16/26	–
Mehar *et al*. (2013)	1/13	5/13	–	3/13	–
Mhada *et al*. (2012)	0/22	5/22	NT	18/22	–
Monjur *et al*. (2010)	0/45	4/45	1/45	1/45	–
Najeeb *et al*. (2012)	1/13	7/13	11/13	11/13	–
Nikkhoo *et al*. (2015)	0/6	0/6	0/6	3/6	–
Ogunlesi *et al*. (2011)	3/25	15/32	15/17	20/33	–
Pius *et al*. (2016)	2/7	2/7	–	7/7	–
Pokhrel *et al*. (2018)		5/20	2/21	–	–
Roy *et al*. (2017)	–	–	–	–	255/1035[2]
Saleem *et al*. (2013)	–	14/104	–	5/104	5/104[1]
Shehab El-Din *et al*. (2015)	0/21	8/21	1/21	1/21	–
Shrestha *et al*. (2010)	–	2/8	5/8	–	–
Shrestha *et al*. (2012)	0/4	–	0/4	–	–
Shrestha *et al*. (2013a)	6/27	6/27	1/27	–	–
Shrestha *et al*. (2013b)	5/8	8/8	8/8	–	–
Softić *et al*. (2017)	0/10	2/10	4/10	4/10	–
Tran *et al*. (2015)	–	9/16	2/16	–	–
Wang *et al*. (2018)	4/96	74/96	–	–	85/96[4]
West and Peterside (2012)	1/21	4/21	–	4/21	–
Yadav *et al*. (2018)	0/9	9/9	0/9	–	–
Zakariya *et al*. (2011)	–	0/33	–	1/33	–

AMP, ampicillin; GEN, gentamicin; CTX, cefotaxime; CRO, ceftriaxone.
[1–3]Combination of 3rd generation cephalosporins; [4]Ceftazidime; [5]Fucloxacillin+Gentamicin; [6]Amoxicillin+Cefotaxime.

sensitivity to the combinations ampicillin plus gentamicin (Table 4).

With the rise of antimicrobial resistance, the treatment of serious bacterial infections in newborns becomes ever more challenging. Adding to this difficulty are the lack of signs and symptoms of neonatal sepsis, as well an adequate empiric treatment regime; the latter being crucial to be able to treat these infections (Roy *et al*. 2107). Ogunlesi *et al*. (2011) reported a rise in mortality in comparison to earlier studies in the same hospital, which correlated to worsening drug resistance. This reinforces the need for a revised empiric antibiotic treatment regime for neonatal sepsis caused by increasing numbers of resistant gram negative strains.

The review found the overall sensitivity to all the empiric antimicrobial agents recommended in the WHO's

Table 2 Sensitivity of *Escherichia coli* to empiric treatment. The columns are arranged by type of antibiotic, represented in an *x/y* format, where '*x*' represents the number of sensitive isolates and '*y*' represents the total number of isolates tested for the particular antibiotic. In some cases, included studies used alternative treatments or a combination of antibiotics, which are indicated in the right-most column. The identity of the therapeutic regimen in this column are indicated by superscript numbers, explained in the footnotes of the table

	AMP	GEN	CTX	CRO	Alternative treatments/ Combination therapy
Adhikari *et al*. (2014)	4/25	17/25	13/25	–	
Anderson *et al*. (2013)	2/11	8/11	–	10/11	
Bandyopadhyay *et al*. (2018)	–	-	8/12*	8/12*	
Bergin *et al*. (2015)	135/258	–	–	–	
Cailes *et al*. (2018)	96/258	220/258	217/258	–	
Chandel *et al*. (2011)	4/21	14/21	10/21		
Datta *et al*. (2014)	–	11/27	6/27	–	
Gkentzi *et al*. (2018)	–	50/54*	45/54*	–	
Guiral *et al*. 2012	13/34	31/34	32/34	–	
Heideking *et al*. (2013)	87/158	151/158	152/158	–	
Jajoo *et al*. (2018)	–	15/32	8/32	8/32	
Jiang *et al*. (2016)	–	17/25	7/25	–	
Kabwe *et al*. (2016)	0/5	0/5	0/5	–	
Kamath *et al*. (2010)	18/26	8/26	–	–	
Kangozhinova *et al*. (2013)	–	1/3	–	0/3	
Kruse *et al*. (2013)	3/21	9/21	9/21	–	
Li *et al*. (2019)	7/25	23/33	17/32	13/23	
Lu *et al*. (2016)	30/121	85/121	72/121	–	
Mehar *et al*. (2013)	3/11	4/11	–	0/11	
Mhada *et al*. (2012)	1/14	8/14	–	12/14	
Monjur *et al*. (2010)	1/14	3/14	2/14	1/14	
Muller-Pebody *et al*. (2011)	–	–	224/236	–	231/236[3], 219/236[4]
Najeeb *et al*. (2012)	8/30	12/30	21/30	16/30	
Nikkhoo *et al*. (2015)	1/3	1/3	2/3	1/3	
Ogunlesi *et al*. (2011)	7/11	10/18	4/5	10/16	
Pius *et al*. (2016)	2/9	8/9	–	9/9	
Pokhrel *et al*. (2018)	–	1/3	0/3	–	
Roy *et al*. (2017)	–	–	–	–	178/342[1]
Shakir *et al*. (2014)	6/24	20/24	24/24	24/24	
Shehab El-Din *et al*. (2015)	0/4	2/4	1/4	1/4	
Shrestha *et al*. (2010)	–	2/4	3/4	–	
Shrestha *et al*. (2013a)	–	3/6	2/6	–	
Shrestha *et al*. (2013b)	1/1	1/1	1/1	–	
Softić *et al*. (2017)	0/7	3/7	3/7	6/7	
Vergnano *et al*. (2011)	–	49/56	–	41/56	
Vergnano *et al*. (2011)	–	–	–	–	27/32[5], 31/36[6]
Wang *et al*. (2018)	17/105	53/105	–	–	65/105[2]
Wu *et al*. (2009)	4/9	6/9	–	–	
Yadav *et al*. (2018)	2/4	4/4	2/4	–	
Zakariya *et al*. (2011)	0/1	0/1	–	0/1	

AMP, ampicillin; GEN, gentamicin; CTX, cefotaxime; CRO, ceftriaxone.
[1]3rd generation cephalosporins; [2]Ceftazidime; [3]Amoxicillin+CTX; [4]Amoxicillin+GEN; [5]Amoxicillin+CTX; [6]Flucloxacillin+GEN.

Pocket Book of Hospital Care for Children (Wakai *et al*. 1996) to be low. Most striking was the high resistance to ampicillin. The treatment regime of ampicillin plus gentamicin would, therefore, in the majority of the cases not be sufficient as an empiric treatment for neonatal sepsis caused by *Enterobacteriaceae*. The broad-spectrum third-generation cephalosporins also showed high rates of resistance, although to a lesser extent compared to ampicillin and gentamicin, except in the case of *Enterobacter* where 16 out of 17 studies showed <50% sensitivity to a third-generation cephalosporin.

The findings of an almost universal resistance to ampicillin have been discussed by some authors to be a consequence of its use in treating early-onset neonatal sepsis,

Table 3 Sensitivity of *Enterobacter* spp. to empiric treatment. The columns are arranged by type of antibiotic, represented in an *x/y* format, where '*x*' represents the number of sensitive isolates and '*y*' represents the total number of isolates tested for the particular antibiotic. In some cases, included studies used alternative treatments or a combination of antibiotics, which are indicated in the right-most column. The identity of the therapeutic regimen in this column are indicated by superscript numbers, explained in the footnotes of the table

	AMP	GEN	CTX	CRO	Alternative treatments/ Combination therapy
Cailes *et al*. (2018)	–	–	–	–	58/99[1] 87/106[2]
Datta *et al*. (2014)	–	1/8	0/8	–	–
Gkentzi *et al*. (2019)	–	28/33	21/33	–	–
Jajoo *et al*. (2018)	–	7/23	7/23	7/23	–
Kamath *et al*. (2010)	10/25	12/25	–	–	–
Kangozhinova *et al*. (2013)	–	2/8	–	3/8	–
Kruse *et al*. (2013)	1/16	6/16	6/16	–	–
Mehar *et al*. (2013)	–	1/3	–	2/4	–
Monjur *et al*. (2010)	0/2	1/2	1/2	1/2	–
Najeeb *et al*. (2012)	1/6	2/6	1/6	1/6	–
Nikkhoo *et al*. (2015)	1/11	4/11	6/11	5/11	–
Pokhrel *et al*. (2018)	–	8/13	2/12	–	–
Shehab El-Din *et al*. (2015)	0/1	1/1	0/1	0/1	–
Shrestha *et al*. (2010)	–	13/29	9/29	–	–
Shrestha *et al*. (2012)	–	0/1	–	–	–
Shrestha *et al*. (2013a)	3/10	2/10	3/10	–	–
Softić *et al*. (2017)	0/2	1/2	1/2	1/2	–
Tran *et al*. (2015)	–	3/5	1/4	–	–
Wang *et al*. (2018)	8/18	10/18	–	–	–
Yadav *et al*. (2018)	–	6/6	1/6	–	–
Zakariya *et al*. (2011)	0/3	0/3	–	0/3	–

AMP, ampicillin; GEN, gentamicin; CTX, cefotaxime; CRO, ceftriaxone.
[1]Ampicillin+CTX; [2]Flucloxacillin+GEN.

frequently caused by group B *streptococcus* (Domonoske and Severson, 2009). Penicillin is also used prophylactically in mothers colonized by group B *streptococcus* before birth (Domonoske and Severson, 2009). The screening programme and prophylactic treatment have had great success in lowering the incidence of early-onset neonatal sepsis caused by group B streptococcus, but has caused an overall increase in the incidence of *Escherichia coli*, specifically in the number of clinical isolates resistant to ampicillin (Domonoske and Severson, 2009). The findings of Bizzarro *et al.* (2008) coincide with previous work, in that they found a significant increase in the number of ampicillin-resistant *E. coli* isolates from neonatal patients with early-onset sepsis (from a very low birth weight population; $P = 0{\cdot}005$), however, this was not the case in isolates from late-onset *Escherichia coli* neonatal infections ($P = 0{\cdot}188$). In summary, it appears that prophylactic ampicillin, whilst being beneficial to lowering early-onset sepsis in neonates, may increase the possibility of late-onset sepsis by antibiotic-resistant *E. coli*.

According to Kabwe *et al.* (2016), the primary cause of resistance in neonatal sepsis is the plasmid-driven extended-spectrum β-lactamases (ESBL), causing resistance to both first- and second-line empiric treatments (Storberg, 2014; Kabwe *et al.* 2016). Supporting this was the finding of an outbreak of multidrug resistant *Klebsiella pneumoniae* (Kabwe *et al.* 2016). Muller-Pebody *et al.* (2011), also warn of the dangers in empiric treatment plans using broad-spectrum third-generation cephalosporins, especially as monotherapy, as it might further drive ESBL producing bacteria by selective pressure. This has been reported in Anderson *et al.* (2014), where a high rate of ampicillin-resistance among *Escherichia coli* was found. However, the high presence of ESBL producers in the centre made it difficult to change the empiric treatment from the less-sensitive ampicillin to a more sensitive third-generation cephalosporin, due to the risk of worsening the already difficult situation with antimicrobial resistance. Studies conducted in the 1990s showed an increase in ESBL producing *Enterobacteriaceae* infections when a third-generation cephalosporin was used as empiric treatment rather than ampicillin (Jain *et al.* 2003; Le *et al.* 2008). West and Peterside (2012) also point at the prohibitive cost of third-generation cephalosporins, another important element to consider when implementing an empiric antibiotic treatment regime, especially in low- to middle-income countries. However,

Table 4 Sensitivity pattern of Enterobacteriaceae as a total. The columns are arranged by type of antibiotic, represented in an *x*/*y* format, where '*x*' represents the number of sensitive isolates and '*y*' represents the total number of isolates tested for the particular antibiotic. In some cases, included studies used alternative treatments or a combination of antibiotics, which are indicated in the right-most column. The identity of the therapeutic regimen in this column are indicated by superscript numbers, explained in the footnotes of the table

	AMP	GEN	CTX	AMX/AMP+CTX	AMX/AMP+GEN	Fluclox+GEN
Gyawali and Sanjana (2013)	5/75	23/75	16/75	–	–	–
Labi *et al*. (2016)	–	–	–	75/149	44/145	–
Lutsar *et al*. (2014)	1/21	13/21	14/21	–	–	–
Muller-Pebody *et al*. (2012)	–	–	215/311	233/311	295/311	–
Vergnano *et al*. (2011)	–	–	–	34/51	–	62/72

AMP, ampicillin; GEN, gentamicin; CTX, cefotaxime; AMX/AMP+CTX; amoxicillin or ampicillin+cefotaxime; AMX/AMP+GEN, amoxicillin or ampicillin+gentamicin; Fluclox+GEN, flucloxacillin+gentamicin.

the use of third-generation cephalosporins have an important role in the empiric treatment of neonatal sepsis, due to the excellent cerebrospinal fluid penetration of cefotaxime and ceftriaxone, and is, therefore, indicated in the suspicion of meningitis (Anderson *et al*. 2014).

Furthermore, Chandel *et al*. (2011), undertook a study exclusively on ESBL producing Gram-negative bacteria causing neonatal sepsis and found a higher rate of ESBL prevalence in the community compared to local hospitals. Similar findings were described in Jajoo *et al*. (2018), reporting on high levels of antimicrobial resistance in the community, with higher levels of infections by antimicrobial resistance strains in neonates admitted to the neonatal intensive care unit from another centre or from the community, compared to neonates born and admitted in the same centre. This is a cause for concern as it shows that antimicrobial resistance is not only an issue belonging to nosocomial infections, but also occurs in community-acquired infections. There is a need for further investigation to see if the strong association between gram negative bacteria, multi-drug resistant strains and nosocomial infections in late onset sepsis might be changing, especially in low- and middle-income countries (Labi *et al*. 2016).

Many studies showed increased sensitivity to antimicrobial agents other than those recommended by the WHO and thus suggesting the need for a change in the empiric antibiotic treatment. Several studies have either changed or recommended changing the empiric treatment regimes to agents with higher antimicrobial action against the common bacteria. One such option is changing gentamicin for another aminoglycoside, such as amikacin, in cases of gentamicin resistance (Fuchs *et al*. 2018). Li *et al*. (2019), report high sensitivity of *Escherichia coli* and *Klebsiella* spp. to imipenem and meropenem, questioning the option of including these in the first-line treatment. Similar suggestions were made by Kruse *et al*. (2013), in response to the high rate of antimicrobial resistance in gram negative bacteria. However, as stated by Li *et al*. (2019), an ideal antimicrobial agent to be used in an empiric treatment regime is one that covers the most common pathogens and does so without driving further antimicrobial resistance by selective pressure. Carbapenem-resistant *Enterobacteriaceae* is a rising threat (Lee *et al*. 2016), and one must look at the possibility of further increasing this issue with the use of carbapenems in the first-line empiric treatment. This was reported by Saleem *et al*. (2013), who undertook a study on the sensitivity pattern in late-onset sepsis caused by *Klebsiella pneumoniae* done and found a rise in carbapenem resistance with a multidrug resistance pattern. Another problem with implementing these newer antimicrobial agents such as carbapenems is their high cost, and their use may, therefore, be limited in low-income countries (Anderson *et al*. 2014).

Another recommendation of new antibiotic treatment regimes was made by Nikkhoo *et al*. (2015), and Ogunlesi *et al*. (2011), where the use of quinolones as an empiric treatment was discussed. Nikkhoo *et al*. (2015) found high susceptibility of *Klebsiella* spp. to ciprofloxacin, and Ogunlesi *et al*. (2011) also reports a high incidence of *Klebsiella* isolates resistant to the first-line treatment and thus questions whether quinolones might be the most suitable option for an empiric treatment. However, the use of quinolones in children is controversial due to the possibility of induced arthropathy (Ogunlesi *et al*. 2011), and its use in neonatal sepsis caused by resistant strains is, therefore, at best experimental. Nevertheless, some justify its use in treating serious bacterial infections in newborns by the benefits outweighing the risk (Kaguelidou *et al*. 2011; Shrestha *et al*. 2013b), when some centres are left with very few options of antimicrobial agents sensitive to the increasingly resistant Gram-negative bacteria.

A few studies did report findings of *Enterobacteriaceae* sensitive to the current empiric antibiotic treatment regimes; the majority in high-income countries. Out of the 9 studies conducted in high-income countries, 6 studies found more than 50% of the tested isolates to be

sensitive to empiric treatment regimes. In comparison, none of the 9 studies in low-income countries was sensitive to some or all of the antimicrobial agents in the treatment regimes. The three studies conducted in the United Kingdom (Muller-Pebody *et al.* 2011; Vergnano *et al.* 2011; Cailes *et al.* 2018) show adequate coverage of current empiric regimes and advice on not altering the empiric regimes from ampicillin plus gentamicin to more broad-spectrum third-generation cephalosporins due to the threat of a further increase in antimicrobial resistance. However, not all studies in high-income countries employed the WHO's recommended antibiotic treatment regimes, and several studies included amoxicillin rather than ampicillin (Muller-Pebody *et al.* 2011; Vergnano *et al.* 2011; Cailes *et al.* 2018).

Seen from a global perspective, the empiric antibiotic treatment recommended by the WHO appears to no longer provide optimal cover of neonatal sepsis caused by *Enterobacteriaceae*, and several of the studies included in this systematic review concluded that the WHO's recommendations ought to be reviewed (Vergnano *et al.* 2011; Viswanathan *et al.* 2011; Lutsar *et al.* 2014; Labi *et al.* 2016).

Limitations

Only a minority (9/48) of the studies presented separate data for late-onset sepsis. Additionally, the definition of the condition varied between the studies. There was no consensus with regard to the percentage of isolates that should be sensitive to a regime for it to be successful. Some authors argue that it should be an overall sensitivity of 95% or higher due to the serious and life-threatening nature of the infection (Kim *et al.* 2002; Marando *et al.* 2018). In this review, a cut-off was made at 50%—an antimicrobial agent was only deemed suitable when over 50% of the tested isolates were sensitive to a said antimicrobial agent. Further limitations of the review include the heterogeneity of the study population, as well as a broad spectrum of inclusion criteria and laboratory diagnostic procedures.

Conclusion

The current first and second-line empiric antibiotic treatment for neonatal sepsis as recommended by WHO in the *Pocket Book of Hospital Care for Children* (Wakai *et al.* 1996) do not provide adequate cover for neonatal sepsis caused by *Enterobacteriaceae*, with some exceptions in high-income countries.

The importance of local epidemiology studies cannot be stressed enough. We demonstrate a large variation in aetiology and antimicrobial resistance at local, regional and international levels. Empiric antibiotic treatment should be customized to each centres' bacterial flora, local prevalence and antimicrobial resistance pattern. However, these studies are time-consuming and need to be repeated frequently to track changes and outbreaks, thus not commonly feasible.

We recommend regularly updating and revising antibiotic-use guidelines. Data from recent studies have indicated the possible substitution of amikacin for gentamicin and considering the inclusion of imipenem and meropenem as first line empiric therapeutic agents; however, more research is required. The implementation of annual reviews of hospital protocols could be crucial in addressing the emerging threat of antimicrobial resistant *Enterobacteriaceae* in neonatal sepsis.

Materials and methods

Outcome measure

The primary outcome of the review is the efficacy of the first (ampicillin and gentamicin) and second-line (third-generation cephalosporins) empiric antibiotic treatment of late-onset neonatal sepsis caused by *Enterobacteriaceae*. The secondary outcome is the variation in sensitivity to the regimes across low-, middle- and high-income countries.

Search strategy

Articles were searched via *Pubmed* and conducted with the three different search strings as presented in Data S1. The PRISMA method was used to carry out the review and the inclusion and exclusion criteria can be found in Table S3.

Due to the unspecific nature of neonatal sepsis, studies reporting on blood stream infections as well as other serious bacterial infections in neonates were included. Studies including cultures from other sites than blood were also included, but when a distinction was made between culture sites only the antimicrobial sensitivity pattern from pathogens identified in blood cultures was included.

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Ethics declarations

This systematic review was carried out in accordance with the Helsinki guidelines and approved by the Ethics Committee of CEU Cardenal Herrera University (authorization number CEI19/149).

Data sharing

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Author contributions

ABA, CCS and VV developed the initial project design. ABA performed the searches and carried out the data filtering. ABA, CCS and VV carried out the final selection of included articles. ABA carried out the data extraction and prepared the first draft of the manuscript. CCS and VV reviewed, edited and prepared the final manuscript. All authors reviewed and gave approval for submission of the final manuscript.

Conflict of Interest

The authors declare no conflict of interest to declare.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1 Detailed information about the included articles in this review.

Table S2 Pathogen distribution. LOS: late-onset sepsis. Total: total included in the study.

Table S3 Inclusion and exclusion criteria.

Data S1 Search strings employed for the preparation of this review.

