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REVIEW ARTICLE

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Neonatal multidrug-resistant gram-negative infection: epidemiology, mechanisms of resistance, and management

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Infants admitted to the neonatal intensive care unit, particularly those born preterm, are at high risk for infection due to the combination of an immature immune system, prolonged hospitalization, and frequent use of invasive devices. Emerging evidence suggests that multidrug-resistant gram-negative (MDR-GN) infections are increasing in neonatal settings, which directly threatens recent and ongoing advances in contemporary neonatal care. A rising prevalence of antibiotic resistance among common neonatal pathogens compounds the challenge of optimal management of suspected and confirmed neonatal infection. We review the epidemiology of MDR-GN infections in neonates in the United States and internationally, with a focus on extended-spectrum β-lactamase (ESBL)-producing *Enterobacterales* and carbapenem-resistant *Enterobacterales* (CRE). We include published single-center studies, neonatal collaborative reports, and national surveillance data. Risk factors for and mechanisms of resistance are discussed. In addition, we discuss current recommendations for empiric antibiotic therapy for suspected infections, as well as definitive treatment options for key MDR organisms. Finally, we review best practices for prevention and identify current knowledge gaps and areas for future research.

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IMPACT:

- Surveillance and prevention of MDR-GN infections is a pediatric research priority.
- A rising prevalence of MDR-GN neonatal infections, specifically ESBL-producing *Enterobacterales* and CRE, compounds the challenge of optimal management of suspected and confirmed neonatal infection.
- Future studies are needed to understand the impacts of MDR-GN infection on neonatal morbidity and mortality, and studies of current and novel antibiotic therapies should include a focus on the pharmacokinetics of such agents among neonates.

INTRODUCTION

Antibiotic resistance is one of the biggest threats to human health.[1,2] Over the past two decades, the prevalence of certain multidrug-resistant gram-negative (MDR-GN) bacteria increased dramatically in patient care settings, including pediatric and neonatal units.[3–8] In 2019, the United States (US) Centers for Disease Control and Prevention (CDC) identified MDR-GN infections, specifically extended-spectrum β-lactamase (ESBL)-producing *Enterobacterales* (formerly *Enterobacteriaceae*[9]) and carbapenem-resistant *Enterobacterales* (CRE), as serious and urgent threats, respectively.[2] In addition, expert collaboration stemming from the CDC-sponsored Prevention Epicenters Program identified the prevention of MDR-GN infections as a top pediatric research priority in 2020.[10]

Newborns admitted to the neonatal intensive care unit (NICU), particularly those born preterm, are at high risk of infection for several reasons, including relative immunocompromise from an immature immune system, prolonged hospitalization, and frequent use of invasive devices and antibiotics.[11] Recent reports demonstrate high rates of neonatal MDR-GN colonization, increasing prevalence of neonatal MDR-GN infections, and MDR-GN outbreaks in neonatal settings.[12,13] These infections are especially problematic in neonates, given the lack of data for treatment options compared with adults and older pediatric patients, compounded by a dwindling antibiotic pipeline, putting them at risk for resistant infections with limited or no antibiotic therapies.[14]

Here, we analyze the contemporary epidemiology of neonatal MDR-GN infections in the US and internationally. We focus on ESBL-producing *Enterobacterales* and CRE, which are two of the most pressing gram-negative resistance threats. Current knowledge is reviewed regarding risk factors for and mechanisms of

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neonatal-resistant infection. We highlight up-to-date recommendations for empiric antibiotic therapy for suspected neonatal infection in light of increasing resistance, as well as definitive treatment options for these key MDR organisms. Finally, we review best practices for prevention and identify current knowledge gaps and areas for future research.

EPIDEMIOLOGY OF NEONATAL INFECTIONS

The epidemiology of neonatal infections is traditionally approached by distinguishing early-onset infection (EOI; first 3 days after birth) and late-onset infection (LOI; after 3 days). The microbiology of these infections varies by geographical region and is evolving over time. In the US and most high-income countries, the two most frequently identified pathogens in EOI are Group B *Streptococcus* (most common in term infants) and *Escherichia coli* (most common in preterm infants). Although these two organisms predominate, approximately one-third of EOI is caused by a variety of other gram-positive and gram-negative bacteria and fungi.[15–17] Among infants with LOI in the US, gram-positive pathogens including coagulase-negative *Staphylococcus* (CONS) species and *Staphylococcus aureus* typically predominate.[5,18–20] Gram-negative bacteria are responsible for approximately 15–30% of LOIs, with *E. coli* and *Klebsiella* species most frequently identified.[5,18–20] In low- and middle-income countries (LMIC), gram-negative bacteria are more commonly identified.[5,21,22] In multicenter longitudinal studies from China and Brazil, more than half of LOIs were caused by gram-negative bacteria, mainly *Enterobacterales*.[23,24] Almost 40% of neonatal infections in sub-Saharan Africa and two-thirds in India are caused by gram-negative pathogens.[25,26] Geographical differences in microbiology are likely related to a diverse prevalence of maternal risk factors (including human immunodeficiency virus), neonatal risk factors such as prematurity, differences in obstetric and neonatal healthcare practices, and regional variation in community flora.[25] Collectively, these data demonstrate the significant burden of infections due to *Enterobacterales* among neonates, particularly in LMIC and among infants with LOI.

MECHANISMS OF ANTIBIOTIC RESISTANCE IN *ENTEROBACTERALES*

While antibiotic resistance among the *Enterobacterales* can manifest by a variety of mechanisms, the following discussion focuses on the epidemiologically important β-lactamase enzymes, as these are the most common and epidemiologically significant resistance determinants.[2,27] β-Lactamases can be encoded by chromosomal genes or by genes present on nonchromosomal and extrachromosomal elements, such as plasmids and transposons. The latter are highly transmissible and largely responsible for the worldwide dissemination of ESBLs and carbapenemase enzymes. Two classification schemes exist for β-lactamases: the Ambler system, which categorizes β-lactamases based on the structure of their active site, and the Bush–Jacoby–Medeiros system, which categorizes β-lactamases based on function and susceptibility to β-lactamase inhibitors (Table 1).[28] Regardless of the type, all β-lactamase enzymes exert their mechanism of action through hydrolysis of the amide bond within the β-lactam ring of β-lactam antibiotics.

Nonenzymatic mechanisms of resistance also contribute to extended-spectrum cephalosporin and carbapenem resistance. These generally result in decreased intracellular concentrations of antibiotics and include porin mutations and the production of efflux pumps. Porins are channels within the bacterial cell membrane that allow antibiotics to traverse the bacterial cell wall.[29,30] Alterations in porins are generally due to mutations in genes encoding outer membrane proteins.[31–33] Efflux pumps function to actively remove antibiotics from the bacterial cell and may confer resistance to multiple different classes of

Table 1. Summary of major extended-spectrum β-lactamase and carbapenemase enzymes.

Ambler class	Type of β-lactamase	Active site	Key example (s)	Typical β-lactam resistance profile	β-lactamase inhibitors	Geographic distribution
Class A	Penicillinase	Serine	KPC CTX-M	Resistant to all cephalosporins and carbapenems (variably elevated meropenem MIC) Resistant to all cephalosporins and monobactams; susceptible to carbapenems	AVI, REL, VAB AVI, CLAV	Global Global
Class B	Metallo-β-lactamase (MBL)	Zinc	NDM VIM IMP	Resistant to all β-lactams except cefiderocol; may retain susceptibility to monobactams, but coproduction of class A ESBLs is common, limiting the utility of monobactams unless combined with an active β-lactamase inhibitor	None	NDM-1: India, Pakistan, Balkan states VIM: Mediterranean basin IMP: Japan, Southeast Asia
Class D	Oxacillinase	Serine	OXA-48-like	Resistant to penicillins, carbapenems; may retain susceptibility to cephalosporins, but ESBLs are often coproduced and lead to cephalosporin resistance	AVI	Mediterranean basin, Middle east

KPC Klebsiella pneumoniae carbapenemase, *MIC* minimum inhibitory concentration, *AVI* avibactam, *REL* relebactam, *VAB* vaborbactam, *CLAV* clavulanate, *NDM* New Delhi metallo-β-lactamase, *VIM* Verona integron-encoded metallo-β-lactamase, *IMP* active on imipenem, *OXA* oxacillinase.

antibiotics, resulting in an MDR phenotype.[34] AcrAB-TolC is a clinically important efflux pump produced by *Enterobacterales* species resulting in an MDR phenotype.[35]

Extended-spectrum β-lactamases

ESBL genes are most often found in *E. coli*, *K. pneumoniae, K. oxytoca*, and *Proteus mirabilus*.[36,37] They are Ambler class A β-lactamases and inactivate most penicillins, cephalosporins, and aztreonam, but retain susceptibility to carbapenems. ESBL enzymes do not directly cause resistance to other non-β-lactam antibiotics such as fluoroquinolones, aminoglycosides, or trimethoprim-sulfamethoxazole, but other genes conferring resistance to these antibiotics are often identified in organisms with ESBL genes.[38–40] The most prevalent ESBL gene is *CTX-M*, and more specifically, *CTX-M-15*, which includes the highly successful clonal lineage *E. coli* sequence type 131.[37,41–44] Other common β-lactamase enzymes include SHV and TEM; while the majority of these enzymes hydrolyze narrow-spectrum cephalosporins, these genes can result in an ESBL phenotype in the presence of point mutations.[37]

Operationally, ceftriaxone nonsusceptibility, defined by the Clinical and Laboratory Standards Institute as a ceftriaxone minimal inhibitory concentration (MIC) of ≥2 μg/μL, is used by many microbiology labs and clinicians as a surrogate for ESBL production.[45] While this approach is highly sensitive for identifying ESBL-producing organisms and can be used clinically for making treatment decisions, other mechanisms of resistance, including AmpC production or nonenzymatic mechanisms of resistance, can also produce a phenotype of ceftriaxone nonsusceptibility.[36,46,47] Some facilities may elect to use a rapid molecular diagnostic testing platform to identify CTX-M-producing isolates; while these assays are specific for ESBL production, a lack of detection of *CTX-M* does not rule out the presence of an alternative ESBL enzyme or confirm ceftriaxone susceptibility.[47–49]

CRE and carbapenemases

The CDC defines CRE as any member of the *Enterobacterales* order that exhibits resistance to ertapenem, meropenem, or imipenem, or produces a carbapenemase enzyme.[50] This definition is agnostic to the mechanism of carbapenem resistance, which can occur either by (1) the production of a carbapenemase or (2) the production of an ESBL or AmpC β-lactamase in combination with impaired membrane permeability from porin mutations or production of drug efflux pumps.[51,52] Differentiation of these two resistance mechanisms is important for epidemiologic purposes, as carbapenemase genes are highly transmissible and associated with hospital outbreaks, including in the NICU setting.[53,54] The Carba NP test and the modified carbapenem inactivation method identify the presence or absence of a carbapenemase gene. Molecular assays can utilize polymerase chain reaction or microarray-based technology to identify specific carbapenemase genes.[55]

While *K. pneumoniae* is the most common bacterium capable of harboring carbapenem resistance enzymes (carbapenem-resistant *K. pneumoniae* [CRKP]), carbapenemase enzymes are also commonly found in other *Enterobacterales* species including *K. aerogenes* (formerly *Enterobacter aerogenes*), *E. coli*, and *E. cloacae*.[51,56] Common carbapenemase enzymes include the Ambler class A serine carbapenemase *K. pneumoniae* carbapenemase (KPC), which is most common in the US and worldwide; the Ambler class B metallo-β-lactamases including the New Delhi metallo-β-lactamase (NDM), imipenem-hydrolyzing metallo-β-lactamases (IMP), and Verona integron-encoded metallo-β-lactamase (VIM); and the Ambler class D oxacillinases (e.g., OXA-48-like).[57] These enzymes differ in regional prevalence and in the extent to which they are inhibited by various β-lactamase inhibitors (Table 1).[58]

EPIDEMIOLOGY OF NEONATAL ANTIBIOTIC-RESISTANT INFECTIONS

The term MDR-GN is used variably and can signify resistance to a certain number of antibiotics, antibiotic classes, combinations of antibiotics, or to the presence of specified resistance determinants (i.e., ESBL, KPC, or other carbapenemase enzymes).[59] This leads to variable estimates of prevalence across centers and regions.[59,60] Further, studies may report rates of colonization, infection, or both. For the purposes of this review, we will refer to specific drug-resistant pathogens to the extent possible (e.g., ESBLs, CRE, or by resistance to specific drugs) and otherwise define MDR-GN as an all-encompassing term. Most studies reporting antimicrobial resistance in NICUs are single-center reports of screening or infection outbreaks. While multicenter collaborative and national surveillance-based efforts to document neonatal infection do exist, they often have limited or no antimicrobial susceptibility data or pathogen resistance testing. Table 2 lists a summary of studies reporting neonatal MDR-GN colonization and/or infection rates, separated into international reports and reports from the US; to reflect contemporary epidemiology, only studies published since 2010 are included.

Resistance to first-line antibiotics

Resistance to conventional first-line antibiotics for common neonatal infections, including ampicillin, gentamicin, cephalosporins, and piperacillin-tazobactam, varies among neonatal gram-negative pathogens.[61,62] Studies from the US demonstrate that isolate resistance to standard antibiotics in NICUs is common (Table 2). For instance, a multicenter study conducted in four tertiary care NICUs in the US found that one-quarter of neonatal gram-negative pathogens were nonsusceptible to ≥1 commonly used antimicrobials, including gentamicin, piperacillin-tazobactam, third- and fourth-generation cephalosporins, and carbapenems.[63] A report of 721 infants with *E. coli* infection admitted to NICUs from 2009 to 2017 in the Premier Health Database found that 67% of isolates were nonsusceptible to ampicillin and 17% were nonsusceptible to aminoglycosides; for EOI caused by *E. coli*, approximately 10% were nonsusceptible to both ampicillin and gentamicin.[61] Stoll et al. similarly reported 7.8% of EOI *E. coli* in the Neonatal Research Network from 2015 to 2017 were resistant to both ampicillin and gentamicin.[17] Reports from Asia, South America, and Africa demonstrate that 50–80% of screened neonates are colonized with some form of MDR-GN bacteria, with high rates of resistance to commonly used drugs such as ampicillin, aminoglycosides, and cephalosporins (Table 2). In one study from India, over 80% of EOI and 100% of LOI caused by gram-negative bacteria were resistant to either ampicillin, gentamicin, or cefotaxime/ceftazidime.[21]

ESBL-producing *Enterobacterales* and CRE

The emergence of ESBL-producing *Enterobacterales* and CRE in neonatal settings is particularly worrisome because such infections may be resistant to most or all conventional antibiotics.[5,64] Rates of colonization with ESBL-producing *Enterobacterales* are variable, but can be substantial; an Ecuadorian study found that more than half of NICU infants were ESBL-colonized.[65] Colonization with carbapenem-resistant organisms is less common. Studies from India and Cambodia found 5–9% of screened infants were colonized with a carbapenem-resistant organism (Table 2).[66–68] In the US, rates of neonatal ESBL-producing *Enterobacterales* remain low, and neonatal CRE is rare. In two New York NICUs, <1% of admitted infants were colonized with ESBL phenotype bacteria, and a study of four NICUs in the US found that <1% of gram-negative isolates were nonsusceptible to carbapenems.[63,69] The Premier report found that 5% of *E. coli* were ESBL phenotype, and none were resistant to carbapenems.[61]

Table 2. Summary of studies reporting neonatal MDR-GN bacteria colonization and/or infection rates.

Author(s)	Publication year	Region/country	Focus	Study size	Key findings
International					
Mitra et al.[148] (abstract)	2011	England and Wales	Cross-sectional survey on the occurrence of ESBL infection	198 units invited to complete the survey	• 35/133 (26%) units reported ESBL-positive results within the 2 years' prior • ESBL-producing *E. coli* and *Klebsiella* species were the most common
Viswanathan et al.[21]	2011	India	MDR-GN organisms causing EOI/LOI	158 infants	• Over 80% of EOI GN organisms were MDR • 100% of LOI GN organisms were MDR
Nordberg et al.[65]	2013	Ecuador	Carriage of ESBL	73 infants	• 56% were colonized with ESBL • Multiple colonization found in 27% (11/41)
Benenson et al.[144]	2013	Israel	Carriage of ESBL *K. pneumoniae*	1763 infants	• Proportion of neonates acquiring ESBL-producing *K. pneumoniae* decreased from 24% in 2006 to 14% in 2007 with active surveillance and isolation precautions/protocols
Rettedal et al.[81]	2013	Norway	Carriage of ESBL-producing *K. pneumoniae*	216 infants	• 24% colonized were colonized with ESBL-producing *K. pneumoniae* • 1 infant acquired a clinical infection
Roy et al.[149]	2013	India	Susceptibility of *K. pneumoniae* and *E. coli* isolates	26 isolates	• 60% of *K. pneumoniae* and 75% of *E. coli* were ESBL producers
Denkel et al.[100]	2014	Germany	Carriage of ESBL	209 VLBW infants	• *Klebsiella* spp. and *E. coli* were the most common • 5.7% were colonized with ESBL
Akturk et al.[97]	2016	Turkey	Carriage of CRKP	1671 infants	• 2.6% were colonized with CRKP • Of those colonized, 18% developed subsequent CRKP infection
Naas et al.[150]	2016	Madagascar	Susceptibility of EOI GN isolates	303 infants	• 35/39 E. cloacae and 16/20 *K. pneumoniae* were ESBL producers
Giuffre et al.[94]	2016	Italy	Carriage of MDR-GN	1152 infants	• 28.8% tested positive for intestinal colonization by at least 1 species/genus of MDR-GN • Prevalence of colonization showed a steady upward trend over a 5-year period
Das Choudhury et al.[151]	2018	India	Carriage of CRE (screened on days 0, 3 and 4–10)	300 infants	• 8.7% were colonized with CRE • None were colonized on day 0 • *K. pneumoniae* was the most common
Delhi Neonatal Infection Study collaboration[26]	2016	India	MDR-GN organisms causing EOI/LOI	13,530 infants	• *Acinetobacter* spp were the most common GN and 82% were MDR • 54% of *Klebsiella* spp. and 38% of *E. coli* species were MDR
Turner et al.[67]	2016	Cambodia	Carriage of 3rd gen. cephalosporin or carbapenem-resistant organisms	333 infants	• 85.9% were colonized with ≥1 3rd gen. cephalosporin-resistant organism • 7.5% were colonized with a carbapenem-resistant organism
Pragosa et al.[79]	2017	Portugal	Carriage of ESBL	188 infants	• 9.6% were colonized with ESBL • *K. pneumoniae* and *E. cloacae* were the most common
Nour et al.[95]	2017	Egypt	Carbapenem susceptibility of GN LOI	158 infants with GN LOI	• 37% of GN-LOIs were carbapenem resistant • Most common CRE was *K. pneumoniae*
Singh et al.[68]	2018	India	Carriage of CRE	300 infants	

Table 2 continued

Author(s)	Publication year	Region/country	Focus	Study size	Key findings
					• 8.7% were colonized with CRE • *K. pneumoniae* was the most common
Leikin-Zach et al.[152]	2018	Israel	Carriage of ESBL	639 infants	• 13.6% were colonized with ESBL • *K. pneumoniae* was the most common
Berberian et al.[75]	2019	Argentina	Descriptive report of MDR-GN infections	21 infants	• Most common pathogens were *Acinetobacter baumanii* and CRKP • Mortality was high and related to prematurity and low birth weight
Ding et al.[13]	2019	China	Systematic review of CRE infections (17 studies)	17 studies	• *K. pneumoniae* was the leading cause of neonatal carbapenem-resistant sepsis
Okomo et al.[25]	2019	26 Sub-Saharan Africa countries	Systematic review and meta-analysis of neonatal infection and antimicrobial resistance	151 studies	• *Klebsiella* species and *E. coli* were the most common • Pooled prevalence of nonsusceptibility for *Klebsiella* species: gentamicin (66%), ceftriaxone (49%), cefotaxime (78%), amikacin (14%), ESBL (49–60%), carbapenems (4%) • Pooled prevalence of nonsusceptibility for *E. coli* species: ampicillin (89%), gentamicin (47%), ESBL (12–46%), piperacillin-tazobactam (7%), carbapenems (2 isolates total)
Smith et al.[66]	2020	India	Carriage of MDR-GN	101 VLBW infants	• 68% were colonized with ESBL, and 5% were colonized with CRE
Labi et al.[90]	2020	Ghana	Carriage of MDR-GN	228 infants	• *Klebsiella* species and *E. coli* were the most common • Pathogenic GN were cultured in 76.8% of neonates, and half were MDR
Yin et al.[84]	2021	China	Carriage of and infection from CRE	1230 infants	• 9.2% were colonized with CRE • CRE colonization increased risk of CRE infection
Sands et al.[43]	2021	7 LMIC	MDR-GN isolates causing EOI/LOI	885 isolates	• *Klebsiella* species and *E. coli* were the most common • GN bacteria were resistant to ampicillin (95%), cefotaxime (83%) and ceftriaxone (80%) • GN bacteria were sensitive to meropenem (13%), imipenem (15%) and tigecycline (16%) • 60%) were resistant to both ampicillin and gentamicin
United States					
Smith et al.104	2010	New York City	Carriage of GN with gentamicin susceptibility	698 VLBW infants	• 5% of GN BSI and 16% of GN gastrointestinal tract isolates were nonsusceptible to gentamicin
Macnow et al.[69]	2013	New York City	Carriage of third-generation cephalosporin-resistant GN	1751 infants	• 1% were colonized with third-generation cephalosporin-resistant GN bacteria
Patel et al.[63]	2017	Northeastern US	Susceptibility of GN organisms causing LOI to gentamicin, piperacillin-tazobactam, 3rd gen. cephalosporins, carbapenems	188 infants	• *Klebsiella* spp. and *E. coli* were the most common • 23% of isolates nonsusceptible to at least 1 drug of interest and 5.8% were nonsusceptible to >1 drug • <1% were nonsusceptible to carbapenems

Table 2 continued

Author(s)	Publication year	Region/country	Focus	Study size	Key findings
Stoll et al.[17]	2020	US (Neonatal Research Network)	Susceptibility of EOI *E. coli* isolates	86 isolates	• 7.8% were resistant to both ampicillin and gentamicin • 95.3% susceptible to third-generation cephalosporins • 93.5% susceptible to cefepime
Flannery et al.[61]	2021	US (Premier Health Database)	Susceptibility of *E. coli* isolated from blood, CSF, or urine	721 infants	• 67% nonsusceptible to ampicillin • 17% nonsusceptible to aminoglycosides • 5% with ESBL phenotype • 0% nonsusceptible to carbapenems 10% of EOI nonsusceptible to ampicillin and gentamicin

Only studies published in 2010 or after were included. Carriage detected by fecal/rectal swabs unless otherwise specified.
BSI bloodstream infection, *LMIC* low- and middle-income countries, *MDR-GN* multidrug-resistant gram-negative, *GN* gram-negative, *EOI* early-onset infection, *LOI* late-onset infection, *US* United States, *NICU* neonatal intensive care unit, *CSF* cerebrospinal fluid, *VLBW* very low birth weight, *CRE* carbapenem-resistant Enterobacterales, *CRKP* carbapenem-resistant *Klebsiella pneumoniae*, *ESBL* extended-spectrum β-lactamase.

Neonatal MDR-GN epidemiological themes

Several themes emerge when assessing the epidemiology of neonatal MDR-GN colonization and infection (Table 2). First, the microbiology of neonatal infection is complex, as evidenced by the report from Sands et al. of MDR-GN from seven LMIC identifying 58 different gram-negative bacterial species causing infection.[43] *Escherichia coli* and *Klebsiella* species are the most common MDR-GN organisms in both international and US settings. In particular, *K. pneumoniae* is the most frequently identified CRE. *Acinetobacter baumanii*, a non-*Enterobacterales* gram-negative bacteria, however, appears to be an emerging resistant pathogen of concern and is responsible for infectious outbreaks in NICUs globally.[70–75] Second, rates of neonatal MDR-GN colonization and infection do vary substantially by geographic location. The burden of neonatal MDR-GN bacteria is much greater in LMIC. In the US, rates of ESBL among neonatal pathogens are low, and neonatal CRE are rare. Third, gram-negative resistance, in general, appears to be less of a concern for EOI compared to LOI. This finding has important implications for the empiric management of suspected neonatal infection, which is subsequently discussed. Currently, screening for ESBL-producing *Enterobacterales* and CRE in NICUs is not routinely performed outside the research or outbreak settings, and therefore comprehensive determination of rates of colonization with these important organisms is difficult to perform.[76]

RISK FACTORS

Multiple studies have identified risk factors for both colonization and infection with MDR-GN organisms, specifically ESBL-producing *Enterobacterales* and CRE, in hospitalized neonates (Table 3). Birth weight and gestational age, both markers of prematurity, are the most consistent risk factors identified across studies for infection caused by MDR-GN bacteria. Gestational age <37 weeks and very low birth weight (<1500 g) are independently associated with increased risk of MDR-GN colonization with and/or infection.[5,77–84]

Prolonged duration of hospitalization, associated with both prematurity and severity of illness, is a consistent and significant risk factor.[65,79,80,82,84–89] Molecular epidemiology suggests gradual incorporation of MDR-GN organisms from the hospital environment into the nascent newborn microflora occurs over time.[62] In one study, length of stay of more than 15 days was independently associated with ESBL-producing *K. pneumoniae* infection (adjusted odds ratio [OR] 4.1, 95% confidence interval [CI] [1.2, 14.3]).[77] Similarly, another study found that neonatal MDR-GN carriage was associated with duration of admission before specimen collection (adjusted OR 1.04, 95% CI [1.05, 1.14].[90] Physical proximity to other patients with MDR-GN infection is associated with infection risk.[91–93] Other risk factors have inconsistently been associated with increased risk of MDR-GN colonization or infection (Table 3), including mechanical ventilation,[66,78,80,84,89] central venous catheters and other invasive devices,[66,80,88,89,94] parenteral nutrition,[66,77,89,95] renal disease,[96] and cytopenias.[66,97] Breastfeeding, compared with formula feeding, has been associated with reduced risk for MDR-GN colonization.[94,98]

Prior exposure to third-generation cephalosporins (adjusted OR 5.97; 95% CI [2.37, 15.08]) and carbapenems (adjusted OR 3.60; 95% CI [1.26, 10.29]), were identified in a Taiwanese study as independent risk factors for MDR-GN acquisition.[96] Other studies have similarly found various definitions of prior antibiotic exposures (particularly broad-spectrum therapy) to increase the risk of MDR-GN colonization and infection.[77,80,81,86,88,89,95,97,98] Variably prolonged duration of antibiotic therapy has also been associated with increased risk of neonatal MDR-GN infection.[90] Cumulative exposure to antibiotics appears to be a greater contributing factor for the risk of resistant infection than the specific antibiotics prescribed.[80]

Table 3. Patient- and center-level risk factors for neonatal multidrug-resistant gram-negative bacteria colonization and infection.

Patient-level risk factors	Center-level risk factors
• Prematurity	• Understaffing
• Very low birth weight (<1500 g)	• Overcrowding
• Maternal or neonatal MDR-GN colonization	• History of a prior unit outbreak
• Prolonged hospitalization	• Poor infection control practices
• Physical proximity to another patient with MDR-GN colonization/infection	• High antibiotic consumption
• Prolonged antibiotic therapy	• Contaminated expressed breast milk
• Broad-spectrum antibiotic therapy	• Artificial fingernails worn by healthcare workers
• Central venous catheter and other invasive devices	• Cockroaches harboring MDR-GN bacteria
• Prolonged mechanical ventilation	
• Parenteral nutrition	
• Underlying renal disease	
• Neutropenia/leukopenia/thrombocytopenia	

MDR-GN multidrug-resistant gram-negative.

Maternal prenatal antibiotic exposure is a risk factor for infection caused by ESBL-producing bacteria in infants.[99] Maternal colonization with MDR-GN is also an important risk factor for infant colonization, as suggested by a prospective surveillance study of two NICUs in Germany, which assessed ESBL-producing *Enterobacterales* colonization among mothers and preterm infants.[100] The incidence of ESBL colonization was 6-fold higher among infants born to colonized versus non-colonized mothers.[100] There are case reports of EOI and LOI caused by ESBL-*Enterobacterales* and CRE in infants born to mothers who immigrated from LMIC; in some cases, the mother was known to be colonized.[101,102] Neonatal intestinal MDR-GN colonization for infants requiring intensive care with prolonged hospitalization likely also plays a role. Pessoa-Silva et al. found that previous colonization with ESBL-producing *K. pneumoniae* was an independent risk factor for subsequent infection in neonates (hazard ratio 5.19, 95% CI [1.58, 17.08]).[88] Akturk et al. found that following the detection of colonization, 18.1% of CRKP-colonized patients in the NICU developed systemic CRKP infection with a median time to infection of 7 days.[97] Neonatal colonizing MDR-GN bacteria and subsequent bloodstream pathogens are often concordant, and early MDR-GN colonization leads to long-lasting colonization or recolonization in ~50% of cases.[103,104] Maternal and/or neonatal MDR-GN colonization as a risk factor for subsequent neonatal infection requires further study, as screening may be a strategy for identifying at-risk newborns, refining infection risk assessment, and targeting empiric antibiotic therapies.

Center-level risk factors can also contribute to outbreaks of ESBL infections in NICUs.[44] Predisposing risk factors include unit understaffing, overcrowding, suboptimal infection control practices including hand hygiene, high antibiotic consumption, and history of a prior unit outbreak (Table 3).[44] While the source of the outbreak is not always identified, admission of a single colonized infant with horizontal dissemination is the most commonly reported source of an ESBL outbreak.[44] Other common sources include transfer from contaminated equipment or surfaces and transmission by healthcare providers.[44] An outbreak of ESBL-producing *K. pneumoniae* in a New York City NICU was linked to exposure to a healthcare worker with artificial fingernails.[105] Contaminated expressed breast milk has been identified as the source of an ESBL-producing *K. pneumoniae* outbreak in a Scandinavian NICU.[106] Cockroaches are potential vectors for nosocomial infections in hospital settings including NICUs and demonstrate high levels of colonization with MDR-GN resistant species.[107,108]

EMPIRIC THERAPY

In the NICU, empiric antibiotic therapy is typically separated by the timing of suspected infection (EOI and LOI) and should account for local infection epidemiology and antibiotic susceptibility patterns. Neonatal antibiotic exposure, particularly to broad-spectrum agents, is associated with multiple adverse outcomes across various studies, including subsequent resistant infection, as well as necrotizing enterocolitis, invasive fungal infection, chronic lung disease, and more.[109–113] Prolonged empiric antibiotic treatment is also associated with adverse outcomes, and therefore when appropriately drawn cultures are obtained and remain sterile, antibiotics should be stopped unless an alternative infection source is identified.[110,111,114] As antibiotic resistance among neonatal pathogens becomes more prevalent, continuous surveillance and assessment of both neonatal antibiotic utilization and antibiotic susceptibility profiles are critical.

Early-onset infection

Trials comparing empiric antibiotic regimens for suspected EOI are uncommon and at high risk of bias. A 2021 Cochrane systematic review assessed the effects of different regimens and concluded that current evidence is insufficient to support any antibiotic regimen being superior to another.[115] In the US, for the term and preterm infants with suspected EOI, empiric therapy typically consists of combined ampicillin and gentamicin.[15,16] This provides effective coverage against Group B *Streptococcus*, which remains universally sensitive to ampicillin. Approximately 65–75% of neonatal *E. coli* are resistant to ampicillin and 10% are resistant to gentamicin; for *E. coli* causing EOI, 7–10% are resistant to both of these drugs.[17,61,116] The American Academy of Pediatrics Committee on the Fetus and Newborn recommends, therefore, that while combined ampicillin and gentamicin is the first choice for empiric therapy for suspected EOI, the addition of broader-spectrum therapy should be considered for high-risk critically ill infants while culture results are pending.[15,16] Because ESBL-producing organisms are uncommon causes of EOI in the US, and carbapenem-resistant organisms causing EOI are rare, empiric therapy for these organisms is rarely indicated and could have adverse consequences.[17,61]

Late-onset infection

For suspected LOI, there is no universal recommendation for empiric therapy. Centers should choose an empiric regimen based on the local antibiogram, suspected source of infection based on clinical presentation, illness severity, and risk factors for resistant infection. Many LOI pathogens are susceptible to

antistaphylococcal penicillin (i.e., nafcillin, oxacillin, flucloxacillin) combined with an aminoglycoside (i.e., gentamicin, amikacin) or a third-generation cephalosporin.[117] Vancomycin is frequently used to cover CONS, despite its low virulence and evidence that early, empiric therapy with vancomycin is typically not required.[118–120] A 2021 Cochrane systematic review assessed the effects of different LOI regimens, and similar to the previously discuss EOI Cochrane review, found that all analyzed trials were at high risk for bias and provided low-quality evidence.[121] Prescribers must, therefore, balance the risk of suboptimal empiric coverage with excessive coverage; the issue is complicated by a lack of clarity as to whether suboptimal early coverage impacts relevant clinical outcomes. The World Health Organization recommends ampicillin and gentamicin as first-line therapy for neonatal sepsis in LMIC and third-generation cephalosporins as the second line.[43] Alternative regimens in regions with high resistance rates to these first-line agents may include piperacillin-tazobactam or a fluoroquinolone.[21] The randomized open-label NeoMero1 trial assessed the efficacy of empiric meropenem for suspected LOI compared to standard of care in 18 NICUs and found no evidence of superiority for treatment success or mortality.[122] These findings, coupled with the low prevalence of ESBL-producing organisms, suggest routine empiric carbapenem therapy for suspected LOI is not warranted and should be reserved for specific scenarios such as an outbreak or known colonization. For infants colonized with an MDRN-GN organism, empiric therapy for any suspected LOI should be tailored appropriately.[76,104]

DEFINITIVE THERAPY: CONSIDERATIONS FOR ESBL AND CRE INFECTIONS

Data informing optimal antibiotic therapy for ESBL and CRE infections are limited and primarily derived from studies performed in adults.[123] As with any bacterial infection, definitive treatment decisions for ESBL and CRE infections in neonates should be made based on results of antibiotic susceptibility testing; consideration of the source of infection, including the possibility of a central nervous system seeding; and using antibiotic doses optimized to the neonate's gestational age, renal function, and presence of extracorporal therapies.[124] Given these complexities, in particular for CRE infections, consultation from a pediatric infectious diseases expert and clinical pharmacist is warranted if available.

Treatment of ESBL infections

For the purposes of this discussion, the term ESBL is used to refer to organisms known to harbor ESBL genes based on confirmatory testing as well as those presumed to be ESBL producers based on ceftriaxone nonsusceptibility. The highest quality data informing the treatment of ESBL infections come from the MERINO study, a randomized trial comparing treatment with piperacillin-tazobactam versus meropenem in adults with ceftriaxone non-susceptible *E. coli* or *K. pneumoniae* bacteremia.[46] Originally planned as a non-inferiority trial, the study was terminated early and demonstrated thirty-day mortality of 12.3% in the piperacillin-tazobactam group as compared to 3.8% in the meropenem group.[46] These data support the use of meropenem for ESBL bacteremia and other invasive infections. However, there is controversy surrounding the potential use of piperacillin-tazobactam or cefepime if susceptible to lower inoculum infections, particularly of the urinary tract. This approach in a neonate warrants discussion with an infectious diseases expert and should be reserved for neonates who are clinically improving on these agents, with consideration of whether meningitis or ventriculitis is present. Finally, because ESBL genes do not influence susceptibility to non-β-lactam antibiotics, use of fluoroquinolones, trimethoprim-sulfamethoxazole (in patients not at risk for hyperbilirubinemia), and in the case of cystitis, aminoglycosides can also be considered if in vitro susceptibility is demonstrated.[123]

Treatment of CRE infections

While dose-optimized meropenem appears to be a treatment option for CRE isolates with meropenem MICs ≤4 μg/mL (i.e., isolates meeting the CDC definition for CRE as a result of isolated meropenem resistance), treatment of carbapenemase-producing isolates and isolates with elevated meropenem MICs >4 μg/mL has proven challenging. Historically, clinicians have relied on combinations of antibiotics, often with marginal in vitro susceptibility and significant toxicities, including colistin, polymyxin B, tigecycline, extended infusion carbapenems, and aminoglycosides. However, several novel β-lactam/β-lactamase inhibitors, including ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-cilastatin-relebactam, have emerged as treatments of choice for CRE.[123,125–130] Use of these agents in neonatal populations is complicated by limited data informing optimal dosing, particularly in preterm populations, as well as limited availability in areas with high CRE prevalence. A detailed discussion of these agents is beyond the scope of this review; however, in the following paragraph, we briefly summarize in vitro and clinical data relevant to the treatment of CRE and highlight the pediatric clinical trials underway. We refer the reader to additional information on this topic.[123,131,132]

Ceftazidime-avibactam is a novel β-lactam/β-lactamase inhibitor with excellent activity against KPC- and OXA-48-like-producing CRE as well as non-carbapenemase-producing CRE. While ceftazidime-avibactam itself does not inhibit metallo-β-lactamases, the combination of ceftazidime-avibactam and aztreonam can effectively inhibit these enzymes, making this a preferred combination for these difficult to treat infections.[123] Ceftazidime-avibactam is Food and Drug Administration (FDA) approved for infants 3 months and older.[133,134] A phase 2 study evaluating safety, pharmacokinetics, and tolerability study in neonates and infants age 26 weeks postmenstrual age to <3 months is ongoing (NCT04126031). Clinical data surrounding the use of ceftazidime-avibactam in neonates are limited to case reports.[135,136] Meropenem-vaborbactam is also a β-lactam/β-lactamase in that inhibits KPC enzymes, but not metallo-β-lactamases or OXA-48-like enzymes.[137,138] Meropenem-vaborbactam was FDA approved for patients 18 years and older in 2017. A phase 1 study is evaluating the pharmacokinetics and safety of meropenem-vaborbactam in children from birth to 18 years (NCT02687906). Pediatric data are limited to case reports.[139] Imipenem-cilastatin-relebactam is a β-lactam/β-lactamase inhibitor with activity against KPC-producing CRE, but not metallo-β-lactamase-producing isolates.[140,141] It was approved for use in patients 18 and over by the FDA in 2019. A phase 2/3 study of safety, tolerability, efficacy, and pharmacokinetics in children from birth to 18 years is ongoing (NCT03969901). Finally, cefiderocol is a siderophore cephalosporin with activity against the clinically relevant carbapenemase enzymes, including metallo-β-lactamases.[142] Cefiderocol was approved for use in adults 18 years and over in 2020. Pediatric and neonatal data are extremely limited, but the results of the pharmacokinetic modeling study presented in abstract form demonstrated that doses of 30 and 40 mg/kg in infants <2 months chronological age in neonates with gestational age <32 weeks and ≥32 weeks gestational age, respectively, resulted in similar drug exposure to adults.[143] A phase 2 safety, tolerability, and pharmacokinetic study are underway in infants and children age 3 months to 18 years (NCT04215991, NCT04335539).

PREVENTION

The most essential tool for preventing MDR-GN colonization and infection is limiting horizontal transmission. Basic infection control

procedures include proper hand hygiene and optimal gloving, disinfection, decontamination, and sterilization practices.[76,144] Unit understaffing and overcrowding should be avoided. To decrease selection pressure, NICUs should make efforts to track broad-spectrum antibiotic use and establish guidelines to discourage overuse. NICU-specific antimicrobial stewardship programs are associated with lower antibiotic utilization and are an important component of mitigating resistance.[145] Cephalosporin restriction can reduce the incidence of neonatal ESBL bacterial sepsis.[146]

Isolation and cohorting of infants with ESBL or CRE colonization or infection can reduce horizontal transmission within a center. Although surveillance for these bacteria is not currently the standard of care outside of outbreak and research settings, such steps can be important when infection or colonization is clinically recognized. Maternal and infant screening for ESBL carriage could potentially lead to early detection of infant colonization and subsequent eradication measures.[44] An Israeli study reported that continuous long-term surveillance with cohorting led to a decrease in ESBL-producing *K. pneumoniae* colonization.[144] In a neonatal ESBL or CRE outbreak scenario, prompt control with the eradication of the infecting strain can be achieved with multidisciplinary interventions.[91,93] An interdisciplinary approach in a Hungarian NICU, including updated complex management plans for intubation, antibiotic therapy, bathing, enteral feeding, hand hygiene, and continuous surveillance led to a significant reduction in the average number of infants colonized and infected with ESBL-producing bacteria.[147] Additional strategies to reduce acquisition and transmission of MDR-GN pathogens include ongoing education of stakeholders, accurate microbiology laboratory procedures including rapid notification, prompt initiation of contact precautions, comprehensive environmental cleaning, and use of optimal central line infection prevention bundles.[5]

FUTURE DIRECTIONS

Infants admitted to NICUs are at high risk of infection. MDR-GN infections, particularly those caused by ESBL-producing *Enterobacterales* and CRE, are increasing in this population and are associated with increased risk of morbidity and mortality.[75,83,95] High rates of colonization and infection from resistant gram-negative organisms in LMIC and reports of outbreaks in higher-income countries should serve as warning signs and prompt calls to action. Treatment options for neonatal MDR-GN, especially CRE, infections are limited, and efficacy and safety of novel antibiotics are currently extrapolated from adult data. Accordingly, surveillance and prevention of MDR-GN infections, specifically ESBL and CRE, is a pediatric research priority in healthcare-associated infections and antimicrobial stewardship.[10,12] Studies are needed to understand the relative impacts of colonization and infection with ESBL and CRE on neonatal morbidity, mortality, and longer-term outcomes compared to infections with less resistant organisms. International networks and collaborations focused on surveillance, prevention, management, and outcomes of neonates with ESBL and CRE colonization and infection are urgently needed. Increased precision of neonatal infection diagnostics and continued antibiotic stewardship in neonatal settings may mitigate resistance related to antibiotic overuse. Finally, studies of current and novel antibiotic therapies should include a focus on the pharmacokinetics of such agents among neonates, including those born preterm, to ensure that therapies are both available to infants and administered safely and effectively.

REFERENCES

1. World Health Organization. Antibiotic resistance. (2020). https://www.who.int/news-room/fact-sheets/detail/antibiotic-resistance. Accessed 11 May 2021.
2. US Centers for Centers for Disease Control. Antibiotic resistance threats in the United States. www.cdc.gov/DrugResistance/Biggest-Threats.html Accessed 11 May 2021.
3. Lautenbach, E. & Perencevich, E. N. Addressing the emergence and impact of multidrug-resistant Gram-negative organisms: a critical focus for the next decade. *Infect. Control Hosp. Epidemiol.* **35**, 333–335 (2014).
4. Folgori, L. et al. Epidemiology and clinical outcomes of multidrug-resistant, Gram-negative bloodstream infections in a European tertiary pediatric hospital during a 12-month period. *Pediatr. Infect. Dis. J.* **33**, 929–932 (2014).
5. Patel, S. J. & Saiman, L. Antibiotic resistance in neonatal intensive care unit pathogens: mechanisms, clinical impact, and prevention including antibiotic stewardship. *Clin. Perinatol.* **37**, 547–563 (2010).
6. Kaye, K. S. & Pogue, J. M. Infections caused by resistant Gram-negative bacteria: epidemiology and management. *Pharmacotherapy* **35**, 949–962 (2015).
7. Logan, L. K. et al. Carbapenem-resistant enterobacteriaceae in children. *Emerg. Infect. Res.* **21**, 17–19 (2015).
8. Logan, L. K., Braykov, N. P., Weinstein, R. A. & Laxminarayan, R. Extended-spectrum ß-lactamase-producing and third-generation cephalosporin-resistant Enterobacteriaceae in children: Trends in the United States, 1999-2011. *J. Pediatr. Infect. Dis. Soc.* **3**, 320–328 (2014).
9. Adeolu, M., Alnajar, S., Naushad, S. & Gupta, R. S. Genome-based phylogeny and taxonomy of the 'Enterobacteriales': proposal for Enterobacterales ord. nov. divided into the families Enterobacteriaceae, Erwiniaceae fam. nov., Pectobacteriaceae fam. nov., Yersiniaceae fam. nov., Hafniaceae fam. nov., Morganellaceae fam. nov., and Budviciaceae fam. nov. *Int. J. Syst. Evol. Microbiol.* **66**, 5575–5599 (2016).
10. Coffin, S. E. et al. Pediatric research priorities in healthcare-associated infections and antimicrobial stewardship. *Infect. Control Hosp. Epidemiol.* https://doi.org/10.1017/ice.2020.1267, 1–4 (2020).
11. Collins, A., Weitkamp, J. H. & Wynn, J. L. Why are preterm newborns at increased risk of infection? *Arch. Dis. Child. Fetal Neonatal Ed.* **103**, F391–F394 (2018).
12. Folgori, L. & Bielicki, J. Future challenges in pediatric and neonatal sepsis: emerging pathogens and antimicrobial resistance. *J. Pediatr. Intens. Care* **8**, 17–24 (2019).
13. Ding, Y., Wang, Y., Hsia, Y., Sharland, M., Heath, P. T. Systematic review of carbapenem-resistant Enterobacteriaceae causing neonatal sepsis in China. *Ann. Clin. Microbiol. Antimicrob.* **18**, 36 (2019).
14. Hsu, A. J. & Tamma, P. D. Treatment of multidrug-resistant Gram-negative infections in children. *Clin. Infect. Dis.* **58**, 1439–1448 (2014).
15. Puopolo, K. M., Benitz, W. E. & Zaoutis, T. E. Management of neonates born at ≥35 0/7 weeks' gestation with suspected or proven early-onset bacterial sepsis. *Pediatrics* **142**, e20182894 (2018).
16. Puopolo, K. M., Benitz, W. E. & Zaoutis, T. E. Management of neonates born at ≤34 6/7 weeks' gestation with suspected or proven early-onset bacterial sepsis. *Pediatrics* **142** (2018).
17. Stoll, B. J. et al. Early-onset neonatal sepsis 2015 to 2017, the rise of *Escherichia coli*, and the need for novel prevention strategies. *JAMA Pediatr.* **174**, 1–12 (2020).
18. Vergnano, S. et al. Neonatal infections in England: the NeonIN surveillance network. *Arch. Dis. Child Fetal Neonatal Ed.* **96**, F9–F14 (2011).
19. Makhoul, I. R., Sujov, P., Smolkin, T., Lusky, A. & Reichman, B. Epidemiological, clinical, and microbiological characteristics of late-onset sepsis among very low birth weight infants in Israel: a national survey. *Pediatrics* **109**, 34–39 (2002).
20. Bizzarro, M. J. Seventy-five years of neonatal sepsis at Yale: 1928–2003. *Pediatrics* **116**, 595–602 (2005).
21. Viswanathan, R. et al. Multi-drug resistant Gram negative bacilli causing early neonatal sepsis in India. *Arch. Dis. Child Fetal Neonatal Ed.* **97**, F182–F187 (2012).
22. Zaidi, A. K. M. et al. Hospital-acquired neonatal infections in developing countries. *Lancet* **365**, 1175–1188 (2005).
23. Jiang, S. et al. Epidemiology and microbiology of late-onset sepsis among preterm infants in China, 2015–2018: a cohort study. *Int J. Infect. Dis.* **96**, 1–9 (2020).
24. Couto, R. C. et al. A 10-year prospective surveillance of nosocomial infections in neonatal intensive care units. *Am. J. Infect. Control* **35**, 183–189 (2007).
25. Okomo, U. et al. Aetiology of invasive bacterial infection and antimicrobial resistance in neonates in sub-Saharan Africa: a systematic review and meta-analysis in line with the STROBE-NI reporting guidelines. *Lancet Infect. Dis.* **3099**, 1–16 (2019).
26. Agarwal, R. et al. Characterisation and antimicrobial resistance of sepsis pathogens in neonates born in tertiary care centres in Delhi, India: a cohort study. *Lancet Glob. Health* **4**, e752–e760 (2016).
27. Bush, K. & Bradford, P. A. Epidemiology of β-lactamase-producing pathogens. *Clin. Microbiol. Rev.* **33**, e00047-19 (2020).
28. Bush, K. & Jacoby, G. A. Updated functional classification of β-lactamases. *Antimicrob. Agents Chemother.* **54**, 969–976 (2010).
29. Wise, M. G., Horvath, E., Young, K., Sahm, D. F. & Kazmierczak, K. M. Global survey of *Klebsiella pneumoniae* major porins from ertapenem non-susceptible isolates lacking carbapenemases. *J. Med. Microbiol.* **67**, 289–295 (2018).

30. Doumith, M., Ellington, M. J., Livermore, D. M. & Woodford, N. Molecular mechanisms disrupting porin expression in ertapenem-resistant *Klebsiella* and *Enterobacter* spp. clinical isolates from the UK. *J. Antimicrob. Chemother.* **63**, 659–667 (2009).
31. Tsai, Y. K. et al. *Klebsiella pneumoniae* outer membrane porins OmpK35 and OmpK36 play roles in both antimicrobial resistance and virulence. *Antimicrob. Agents Chemother.* **55**, 1485–1493 (2011).
32. Hamzaoui, Z. et al. Role of association of OmpK35 and OmpK36 alteration and bla ESBL and/or bla AmpC genes in conferring carbapenem resistance among non-carbapenemase-producing Klebsiella pneumoniae. *Int. J. Antimicrob. Agents* **52**, 898–905 (2018).
33. Majewski, P. et al. Altered outer membrane transcriptome balance with AmpC overexpression in carbapenem-resistant enterobacter cloacae. *Front. Microbiol.* **7**, 2054 (2016).
34. Du, D. et al. Multidrug efflux pumps: structure, function and regulation. *Nat. Rev. Microbiol.* **16**, 523–539 (2018).
35. Du, D. et al. Structure of the AcrAB-TolC multidrug efflux pump. *Nature* **509**, 512–515 (2014).
36. Tamma, P. D. et al. Molecular epidemiology of ceftriaxone-nonsusceptible Enterobacterales isolates in an Academic Medical Center in the United States. *Open Forum Infect. Dis.* **6**, ofz353 (2019).
37. Doi, Y., Iovleva, A. & Bonomo, R. A. The ecology of extended-spectrum β-lactamases (ESBLs) in the developed world. *J. Travel Med.* **24**, S44–S51 (2017).
38. Salah, F. D. et al. Distribution of quinolone resistance gene (qnr) in ESBL-producing *Escherichia coli* and *Klebsiella* spp. in Lomé, Togo. *Antimicrob. Resist. Infect. Control* **8**, 104 (2019).
39. López-Diaz, M. D. C. et al. Plazomicin activity against 346 extended-spectrum-β-lactamase/AmpC-producing *Escherichia coli* urinary isolates in relation to aminoglycoside-modifying enzymes. *Antimicrob. Agents Chemother.* **61**, e02454-16 (2017).
40. Poirel, L., Leviandier, C. & Nordmann, P. Prevalence and genetic analysis of plasmid-mediated quinolone resistance determinants QnrA and QnrS in Enterobacteriaceae isolates from a French University Hospital. *Antimicrob. Agents Chemother.* **50**, 3992–3997 (2006).
41. Tsai, M. H. et al. Clinical and molecular characteristics of neonatal extended-spectrum β-lactamase-producing gram-negative bacteremia: a 12-year case-control-control study of a referral center in Taiwan. *PLoS ONE* **11**, e0159744 (2016).
42. Castanheira, M., Farrell, S. E., Deshpande, L. M., Mendes, R. E. & Jones, R. N. Prevalence of β-lactamase-encoding genes among Enterobacteriaceae bacteremia isolates collected in 26 U.S. Hospitals: report from the SENTRY antimicrobial surveillance program (2010). *Antimicrob. Agents Chemother.* **57**, 3012–3020 (2013).
43. Sands, K. et al. Characterization of antimicrobial-resistant Gram-negative bacteria that cause neonatal sepsis in seven low- and middle-income countries. *Nat. Microbiol.* **6**, 512–523 (2021).
44. Stapleton, P. J. M. et al. Outbreaks of extended spectrum beta-lactamaseproducing Enterobacteriaceae in neonatal intensive care units: a systematic review. *Arch. Dis. Child. Fetal Neonatal Ed.* **101**, F72–F78 (2016).
45. Clinical and Laboratory Standards Institute. *Performance Standards for Antimicrobial Susceptibility Testing. An Informational Supplement for Global Application Developed Through the Clinical and Laboratory Standards Institute Consensus Process*, 26th edn (Clinical and Laboratory Standards Institute, 2019).
46. Harris, P. N. A. et al. Effect of piperacillin-tazobactam vs meropenem on 30-day mortality for patients with e coli or *Klebsiella pneumoniae* bloodstream infection and ceftriaxone resistance. *JAMA* **320**, 984–994 (2018).
47. Spafford, K., MacVane, S. & Humphries, R. Evaluation of empiric β-lactam susceptibility prediction among Enterobacteriaceae by molecular β-lactamase gene testing. *J. Clin. Microbiol.* **57**, e00674-19 (2019).
48. Walker, T. et al. Clinical impact of laboratory implementation of verigene BC-GN microarray-based assay for detection of gram-negative bacteria in positive blood cultures. *J. Clin. Microbiol* **54**, 1789–1796 (2016).
49. Rivard, K. R. et al. Impact of antimicrobial stewardship and rapid microarray testing on patients with Gram-negative bacteremia. *Eur. J. Clin. Microbiol. Infect. Dis.* **36**, 1879–187 (2017).
50. CRE|HAI|CDC. CRE technical information. (2019). https://www.cdc.gov/hai/organisms/cre/technical-info.html. Accessed 6 Jun 2021.
51. Guh, A. Y. et al. Epidemiology of carbapenem-resistant enterobacteriaceae in 7 US communities, 2012-2013. *JAMA* **314**, 1479–1487 (2015).
52. van Duin, D. et al. Molecular and clinical epidemiology of carbapenem-resistant Enterobacterales in the USA (CRACKLE-2): a prospective cohort study. *Lancet Infect. Dis.* **20**, 731–741 (2020).
53. Stoesser, N. et al. Genome sequencing of an extended series of NDM-producing *Klebsiella pneumoniae* isolates from neonatal infections in a Nepali hospital characterizes the extent of community- versus hospital-associated transmission in an endemic setting. *Antimicrob. Agents Chemother.* **58**, 7347–7357 (2014).
54. Chabah, M. et al. Healthcare-associated infections due to carbapenemase-producing Enterobacteriaceae: bacteriological profile and risk factors. *Med. Mal. Infect.* **46**, 157–162 (2016).
55. Tamma, P. D. et al. Comparison of 11 phenotypic assays for accurate detection of carbapenemase- producing enterobacteriaceae. *J. Clin. Microbiol.* **55**, 1046–1055 (2017).
56. Arnold, R. S. et al. Emergence of *Klebsiella pneumoniae* carbapenemase-producing bacteria. *South Med. J.* **104**, 40–45 (2011).
57. Kitchel, B. et al. Molecular epidemiology of KPC-producing *Klebsiella pneumoniae* isolates in the United States: clonal expansion of multilocus sequence type 258. *Antimicrob. Agents Chemother.* **53**, 3365–3370 (2009).
58. Logan, L. K. & Weinstein, R. A. The epidemiology of Carbapenem-resistant enterobacteriaceae: the impact and evolution of a global menace. *J. Infect. Dis.* **215**, S28–S36 (2017).
59. Wolfensberger, A., Kuster, S. P., Marchesi, M., Zbinden, R. & Hombach, M. The effect of varying multidrug-resistence (MDR) definitions on rates of MDR Gram-negative rods. *Antimicrob. Resist. Infect. Control* **8**, 1–9 (2019).
60. Drees, M., Pineles, L., Harris, A. D. & Morgan, D. J. Variation in definitions and isolation procedures for multidrug-resistant Gram-negative bacteria: a survey of the Society for Healthcare Epidemiology of America Research Network. *Infect. Control Hosp. Epidemiol.* **35**, 362–366 (2014).
61. Flannery, D. D. et al. Antibiotic susceptibility of *Escherichia coli* among infants admitted to neonatal intensive care units across the US from 2009 to 2017. *JAMA Pediatr.* **175**, 168–175 (2021).
62. Toltzis, P. et al. Molecular epidemiology of antibiotic-resistant gram-negative bacilli in a neonatal intensive care unit during a nonoutbreak period. *Pediatrics* **108**, 1143–1148 (2001).
63. Patel, S. J. et al. Gram-negative Bacilli in infants hospitalized in the neonatal intensive care unit. *J. Pediatr. Infect. Dis. Soc.* https://doi.org/10.1093/jpids/piw032 (2016).
64. Lukac, P. J., Bonomo, R. A. & Logan, L. K. Extended-spectrum β-lactamase-producing enterobacteriaceae in children: old foe, emerging threat. *Clin. Infect. Dis.* **60**, 1389–1397 (2015).
65. Nordberg, V. et al. High proportion of intestinal colonization with successful epidemic clones of ESBL-producing Enterobacteriaceae in a Neonatal Intensive Care Unit in Ecuador. *PLoS ONE* **8**, e76597 (2013).
66. Smith, A., Anandan, S., Veeraraghavan, B. & Thomas, N. Colonization of the preterm neonatal gut with carbapenem-resistant Enterobacteriaceae and its association with neonatal sepsis and maternal gut flora. *J. Glob. Infect. Dis.* **12**, 101–104 (2020).
67. Turner, P. et al. High prevalence of antimicrobial-resistant gram-negative colonization in hospitalized cambodian infants. *Pediatr. Infect. Dis. J.* **35**, 856–861 (2016).
68. Singh, N. P. et al. Predictors for gut colonization of carbapenem-resistant Enterobacteriaceae in neonates in a neonatal intensive care unit. *Am. J. Infect. Control* **46**, e31–e35 (2018).
69. Macnow, T. et al. Utility of surveillance cultures for antimicrobial resistant organisms in infants transferred to the neonatal intensive care unit. *Pediatr. Infect. Dis. J.* **32**, e443–e450 (2013).
70. Gramatniece, A. et al. Control of *Acinetobacter baumannii* outbreak in the neonatal intensive care unit in Latvia: Whole-genome sequencing powered investigation and closure of the ward. *Antimicrob. Resist. Infect. Control* **8**, 84 (2019).
71. Chan, P.-C. et al. Control of an outbreak of pandrug-resistant *Acinetobacter baumannii* colonization and infection in a neonatal intensive care unit. *Infect. Control Hosp. Epidemiol.* **28**, 423–429 (2007).
72. Huang, Y. C. et al. Outbreak of *Acinetobacter baumannii* bacteremia in a neonatal intensive care unit: clinical implications and genotyping analysis. *Pediatr. Infect. Dis. J.* **21**, 1105–1109 (2002).
73. Melamed, R. et al. Successful control of an *Acinetobacter baumannii* outbreak in a neonatal intensive care unit. *J. Hosp. Infect.* **53**, 31–38 (2003).
74. Al Jarousha, A. M. K., Jadba, A. H. N. E., Afifi, A. S. A. & Qouqa, I. A. E. Nosocomial multidrug-resistant *Acinetobacter baumannii* in the neonatal intensive care unit in Gaza City, Palestine. *Int. J. Infect. Dis.* **13**, 623–628 (2009).
75. Berberian, G. et al. Multidrug resistant Gram-negative infections in neonatology. *Arch. Argent. Pediatr.* **117**, 6–11 (2019).
76. Ramirez, C. B. & Cantey, J. B. Antibiotic resistance in the neonatal intensive care unit. *Neoreviews* **20**, e135–e144 (2019).
77. Abdel-Hady, H., Hawas, S., El-Daker, M. & El-Kady, R. Extended-spectrum β-lactamase producing *Klebsiella pneumoniae* in neonatal intensive care unit. *J. Perinatol.* **28**, 685–690 (2008).

78. Huang, Y., Zhuang, S. & Du, M. Risk factors of nosocomial infection with extended-spectrum beta-lactamase-producing bacteria in a neonatal intensive care unit in China. *Infection* **35**, 339–345 (2007).
79. Pragosa, H., Marçal, M., Gonçalves, E., Martins, F. & Lopo-Tuna, M. Multi-drug-resistant Enterobacteriaceae in a Portuguese neonatal intensive care unit. *J. Hosp. Infect.* **96**, 130–131 (2017).
80. Singh, N. et al. Risk of resistant infections with enterobacteriaceae in hospitalized neonates. *Pediatr. Infect. Dis. J.* **21**, 1029–1033 (2002).
81. Rettedal, S., Löhr, I. H., Natås, O., Sundsfjord, A. & Øymar, K. Risk factors for acquisition of CTX-M-15 extended-spectrum beta-lactamase-producing *Klebsiella pneumoniae* during an outbreak in a neonatal intensive care unit in Norway. *Scand. J. Infect. Dis.* **45**, 54–58 (2013).
82. Vijayakanthi, N., Bahl, D., Kaur, N., Maria, A. & Dubey, N. K. Frequency and characteristics of infections caused by extended-spectrum beta-lactamase-producing organisms in neonates: a prospective cohort study. *Biomed. Res. Int.* **2013**, 756209 (2013).
83. Ballot, D. E. et al. A review of -multidrug-resistant Enterobacteriaceae in a neonatal unit in Johannesburg, South Africa. *BMC Pediatr.* **19**, 320 (2019).
84. Yin, L. et al. Carbapenem-resistant Enterobacterales colonization and subsequent infection in a neonatal intensive care unit in Shanghai, China. *Infect. Prev. Pract.* 100147 (2021).
85. Wójkowska-Mach, J. et al. Enterobacteriaceae infections of very low birth weight infants in Polish neonatal intensive care units. *Pediatr. Infect. Dis. J.* **32**, 594–598 (2013).
86. Crivaro, V. et al. Risk factors for extended-spectrum β-lactamase-producing *Serratia marcescens* and *Klebsiella pneumoniae* acquisition in a neonatal intensive care unit. *J. Hosp. Infect.* **67**, 135–141 (2007).
87. Shakil, S., Akram, M., Ali, S. M. & Khan, A. U. Acquisition of extended-spectrum β-lactamase producing *Escherichia coli* strains in male and female infants admitted to a neonatal intensive care unit: molecular epidemiology and analysis of risk factors. *J. Med. Microbiol.* **59**, 948–954 (2010).
88. Pessoa-Silva, C. L. et al. Extended-spectrum β-lactamase-producing *Klebsiella pneumoniae* in a neonatal intensive care unit: risk factors for infection and colonization. *J. Hosp. Infect.* **53**, 198–206 (2003).
89. Boo, N. Y., Ng, S. F. & Lim, V. K. E. A case-control study of risk factors associated with rectal colonization of extended-spectrum beta-lactamase producing *Klebsiella* sp. in newborn infants. *J. Hosp. Infect.* **61**, 68–74 (2005).
90. Labi, A.-K. et al. High carriage rates of multidrug-resistant gram-negative bacteria in neonatal intensive care units from Ghana. *Open Forum Infect. Dis.* **7**, ofaa10 (2020).
91. Cantey, J. B. et al. Prompt control of an outbreak caused by extended-spectrum β-lactamase-producing *Klebsiella pneumoniae* in a neonatal intensive care unit. *J. Pediatr.* **163**, 672–679.e1–3 (2013).
92. Baek, E.-H. et al. Successful control of an extended-spectrum beta-lactamase-producing *Klebsiella pneumoniae* ST307 outbreak in a neonatal intensive care unit. *BMC Infect. Dis.* **20**, 166 (2020).
93. Escobar Pérez, J. A. et al. Outbreak of NDM-1-producing *Klebsiella pneumoniae* in a neonatal unit in Colombia. *Antimicrob. Agents Chemother.* **57**, 1957–1960 (2013).
94. Giuffre, M. et al. The increasing challenge of multidrug-resistant gram-negative bacilli: results of a 5-year active surveillance program in a neonatal intensive care unit. *Medicine* **95**, e3016 (2016).
95. Nour, I. et al. Risk factors and clinical outcomes for carbapenem-resistant Gram-negative late-onset sepsis in a neonatal intensive care unit. *J. Hosp. Infect.* **97**, 52–58 (2017).
96. Tsai, M.-H. et al. Risk factors and outcomes for multidrug-resistant Gram-negative bacteremia in the NICU. *Pediatrics* **133**, e322–e329 (2014).
97. Akturk, H. et al. Carbapenem-resistant *Klebsiella pneumoniae* colonization in pediatric and neonatal intensive care units: risk factors for progression to infection. *Braz. J. Infect. Dis.* **20**, 134–140 (2016).
98. Cassettari, V. C. et al. Risk factors for colonisation of newborn infants during an outbreak of extended-spectrum β-lactamase-producing Klebsiella pneumoniae in an intermediate-risk neonatal unit. *J. Hosp. Infect.* **71**, 340–347 (2009).
99. Kim, J. H. et al. Maternal antibiotic exposure during pregnancy is a risk factor for community-acquired urinary tract infection caused by extended-spectrum beta-lactamase-producing bacteria in infants. *Pediatr. Nephrol.* https://doi.org/10.1007/s00467-021-05163-z (2021).
100. Denkel, L. A. et al. The mother as most important risk factor for colonization of very low birth weight (VLBW) infants with extended-spectrum b-lactamase-producing Enterobacteriaceae (ESBL-E). *J. Antimicrob. Chemother.* **69**, 2230–2237 (2014).
101. Dolma, K. et al. Early-onset neonatal sepsis with extended spectrum beta-lactamase producing *Escherichia coli* in infants born to South and South East Asian Immigrants: a case series. *AJP Rep.* **8**, e277–e279 (2018).
102. Seesahai, J. et al. Neonates with maternal colonization of carbapenemase-producing, carbapenem-resistant Enterobacteriaceae: a mini-review and a suggested guide for preventing neonatal infection. *Children* **8**, 399 (2021).
103. Kock, K. et al. Long-term follow-up after neonatal colonization with extended spectrum beta-lactamase Gram-negative bacteria.*Pediatr Res.* **70**, 457 (2011).
104. Smith, A. et al. Concordance of gastrointestinal tract colonization and subsequent bloodstream infections with Gram-negative bacilli in very low birth weight infants in the neonatal intensive care unit. *Pediatr. Infect. Dis. J.* **29**, 831–835 (2010).
105. Gupta, A. et al. Outbreak of extended-spectrum beta-lactamase-producing *Klebsiella pneumoniae* in a neonatal intensive care unit linked to artificial nails. *Infect. Control Hosp. Epidemiol.* **25**, 210–215 (2004).
106. Rettedal, S. et al. First outbreak of extended-spectrum β-lactamase-producing *Klebsiella pneumoniae* in a Norwegian neonatal intensive care unit; associated with contaminated breast milk and resolved by strict cohorting. *APMIS* **120**, 612–621 (2012).
107. Tilahun, B. et al. High load of multi-drug resistant nosocomial neonatal pathogens carried by cockroaches in a neonatal intensive care unit at Tikur Anbessa specialized hospital, Addis Ababa, Ethiopia. *Antimicrob. Resist. Infect. Control* **1**, 12 (2012).
108. Pai, H.-H., Chen, W.-C. & Peng, C.-F. Cockroaches as potential vectors of nosocomial infections. *Infect. Control Hosp. Epidemiol.* **25**, 979–984 (2004).
109. Cotten, C. M. et al. The association of third-generation cephalosporin use and invasive candidiasis in extremely low birth-weight infants. *Pediatrics* **118**, 717–722 (2006).
110. Cotten, C. M. et al. Prolonged duration of initial empirical antibiotic treatment is associated with increased rates of necrotizing enterocolitis and death for extremely low birth weight infants. *Pediatrics* **123**, 58–66 (2009).
111. Kuppala, V. S., Meinzen-Derr, J., Morrow, A. L. & Schibler, K. R. Prolonged initial empirical antibiotic treatment is associated with adverse outcomes in premature infants. *J. Pediatr.* **159**, 720–725 (2011).
112. Ting, J. Y. et al. Association between antibiotic use and neonatal mortality and morbidities in very low-birth-weight infants without culture-proven sepsis or necrotizing enterocolitis. *JAMA Pediatr.* **170**, 1181 (2016).
113. Novitsky, A. et al. Prolonged early antibiotic use and bronchopulmonary dysplasia in very low birth weight infants. *Am. J. Perinatol.* **32**, 043–048 (2014).
114. Cantey, J. B. & Baird, S. D. Ending the culture of culture-negative sepsis in the neonatal ICU. *Pediatrics* **140**, e20170044 (2017).
115. Korang, S. K. et al. Antibiotic regimens for early-onset neonatal sepsis. *Cochrane Database Syst. Rev.* **5**, CD013837 (2021).
116. Schrag, S. J. et al. Epidemiology of invasive early-onset neonatal sepsis, 2005 to 2014. *Pediatrics* **138**, e20162013 (2016).
117. Muller-Pebody, B. et al. Empirical treatment of neonatal sepsis: Are the current guidelines adequate? *Arch. Dis. Child Fetal Neonatal Ed.* **96**, F4–F8 (2011).
118. Jean-Baptiste, N. et al. Coagulase-negative Staphylococcal infections in the neonatal intensive care unit. *Infect. Control Hosp. Epidemiol.* **32**, 679–686 (2011).
119. Chiu, C. H. et al. Effectiveness of a guideline to reduce vancomycin use in the neonatal intensive care unit. *Pediatr. Infect. Dis. J.* **30**, 273–278 (2011).
120. Hamdy, R. F. et al. Reducing vancomycin use in a level IV NICU. *Pediatrics* **146**, e20192963 (2020).
121. Korang, S. K. et al. Antibiotic regimens for late-onset neonatal sepsis. *Cochrane Database Syst. Rev.* **5**, CD013836 (2021).
122. Lutsar, I. et al. Meropenem vs standard of care for treatment of neonatal late onset sepsis (NeoMero1): a randomised controlled trial. *PLoS ONE* **15**, e0229380 (2020).
123. Tamma, P. D. et al. Infectious Diseases Society of America Guidance on the treatment of extended-spectrum β-lactamase producing Enterobacterales (ESBL-E), carbapenem-resistant Enterobacterales (CRE), and *Pseudomonas aeruginosa* with difficult-to-treat resistance (DTR-*P. aeruginosa*). *Clin. Infect. Dis.* **72**, 1109–1116 (2021).
124. Rivera-Chaparro, N. D., Cohen-Wolkowiez, M. & Greenberg, R. G. Dosing antibiotics in neonates: review of the pharmacokinetic data. *Fut. Microbiol.* **12**, 1001–1016 (2017).
125. Motsch, J. et al. RESTORE-IMI 1: a multicenter, randomized, doubleblind trial comparing efficacy and safety of Imipenem/Relebactam vs Colistin plus imipenem in patients with imipenem-nonsusceptible bacterial infections. *Clin. Infect. Dis.* **70**, 1799–1808 (2020).
126. Shields, R. K. et al. Ceftazidime-avibactam is superior to other treatment regimens against carbapenem-resistant *Klebsiella pneumoniae* bacteremia. *Antimicrob. Agents Chemother.* **61**, https://doi.org/10.1128/AAC.00883-17 (2017).
127. Van Duin, D. et al. Colistin versus ceftazidime-avibactam in the treatment of infections due to carbapenem-resistant Enterobacteriaceae. *Clin. Infect. Dis.* **66**, 163–171 (2018).
128. Wunderink, R. G. et al. Effect and safety of meropenem–vaborbactam versus best-available therapy in patients with carbapenem-resistant enterobacteriaceae

infections: the TANGO II Randomized Clinical Trial. *Infect. Dis. Ther.* **7**, 439–455 (2018).
129. Wunderink, R. G. et al. Cefiderocol versus high-dose, extended-infusion meropenem for the treatment of Gram-negative nosocomial pneumonia (APEKS-NP): a randomised, double-blind, phase 3, non-inferiority trial. *Lancet Infect. Dis.* **21**, 213–225 (2021).
130. Bassetti, M. et al. Efficacy and safety of cefiderocol or best available therapy for the treatment of serious infections caused by carbapenem-resistant Gram-negative bacteria (CREDIBLE-CR): a randomised, open-label, multicentre, pathogen-focused, descriptive, phase 3 trial. *Lancet Infect. Dis.* **21**, 226–240 (2021).
131. Tamma, P. D. & Hsu, A. J. Defining the role of novel β-lactam agents that target carbapenem-resistant gram-negative organisms. *J. Pediatr. Infect. Dis. Soc.* **8**, 251–260 (2019).
132. Chiotos, K., Hayes, M., Gerber, J. S. & Tamma, P. D. Treatment of carbapenem-resistant Enterobacteriaceae infections in children. *J. Pediatr. Infect. Dis. Soc.* **9**, 56–66 (2019).
133. Bradley, J. S. et al. Safety and efficacy of ceftazidime-avibactam plus metronidazole in the treatment of children ≥3 months to <18 years with complicated intra-abdominal infection: results from a Phase 2, Randomized, Controlled Trial. *Pediatr. Infect. Dis. J.* **38**, 816–824 (2019).
134. Bradley, J. S. et al. Safety and efficacy of ceftazidime-avibactam in the treatment of children ≥3 months to <18 years with complicated urinary tract infection: results from a Phase 2 Randomized, Controlled Trial. *Pediatr. Infect. Dis. J.* **38**, 920–928 (2019).
135. Iosifidis, E. et al. Use of ceftazidime-avibactam for the treatment of extensively drug-resistant or Pan drug-resistant *Klebsiella pneumoniae* in neonates and children <5 years of age. *Pediatr. Infect. Dis. J.* **38**, 812–815 (2019).
136. Coskun, Y. & Atici, S. Successful treatment of pandrug-resistant *Klebsiella pneumoniae* infection with ceftazidime-avibactam in a preterm infant: a case Report. *Pediatr. Infect. Dis. J.* **39**, 854–856 (2020).
137. Castanheira, M., Huband, M. D., Mendes, R. E. & Flamm, R. K. Meropenem-vaborbactam tested against contemporary Gram-negative isolates collected worldwide during 2014, including carbapenem-resistant, KPC-producing, multidrug-resistant, and extensively drug-resistant enterobacteriaceae. *Antimicrob. Agents Chemother.* **61**, e00567-17 (2017).
138. Hackel, M. A., Lomovskaya, O., Dudley, M. N., Karlowsky, J. A. & Sahm, D. F. In vitro activity of meropenem-vaborbactam against clinical isolates of KPC-positive Enterobacteriaceae. *Antimicrob. Agents Chemother.* **62**, e01904-17 (2018).
139. Hanretty, A. M. et al. Pharmacokinetics of the meropenem component of meropenem-vaborbactam in the treatment of KPC-producing *Klebsiella pneumoniae* bloodstream infection in a pediatric patient. *Pharmacotherapy* **38**, e87–e91 (2018).
140. Lapuebla, A. et al. Activity of imipenem with relebactam against gGram-negative pathogens from New York City. *Antimicrob. Agents Chemother.* **59**, 5029–5031 (2015).
141. Livermore, D. M., Warner, M. & Mushtaq, S. Activity of MK-7655 combined with imipenem against enterobacteriaceae and *Pseudomonas aeruginosa*. *J. Antimicrob. Chemother.* **68**, 2286–2290 (2013).
142. Zhanel, G. G. et al. Cefiderocol: a siderophore cephalosporin with activity against carbapenem-resistant and multidrug-resistant Gram-negative bacilli. *Drugs* **79**, 271–289 (2019).
143. Katsube, T., Echols, R. & Wajima, T. Prediction of cefiderocol pharmacokinetics and probability of target attainment in pediatric subjects for proposing dose regimens. *Open Forum Infect. Dis.* **6**, S330–S331 (2019).
144. Benenson, S. et al. Continuous surveillance to reduce extended-spectrum β-lactamase *Klebsiella pneumoniae* colonization in the neonatal intensive care unit. *Neonatology* **103**, 155–160 (2013).
145. Prusakov, P. et al. A global point prevalence survey of antimicrobial use in neonatal intensive care units: the no-more-antibiotics and resistance (NO-MAS-R) study. *EClinicalMedicine* **32**, https://doi.org/10.1016/j.eclinm.2021.100727 (2021).
146. Murki, S., Jonnala, S., Mohammed, F. & Reddy, A. Restriction of cephalosporins and control of extended spectrum β-lactamase producing gram negative bacteria in a neonatal intensive care unit. *Indian Pediatr.* **47**, 785–788 (2010).
147. Szél, B. et al. Successful elimination of extended-spectrum beta-lactamase (ESBL)-producing nosocomial bacteria at a neonatal intensive care unit. *World J. Pediatr.* **13**, 210–216 (2017).
148. Mitra, S., Sivakumar, P., Oughton, J. & Ossuetta, I. National surveillance study of extended spectrum lactamase (ESBL) producing organism infection in neonatal units of England and Wales. *Arch. Dis. Child* **96**, A47–A47 (2011).
149. Roy, S. et al. Neonatal septicaemia caused by diverse clones of *Klebsiella pneumoniae* & *Escherichia coli* harbouring blaCTX-M-15. *Indian J. Med. Res.* **137**, 791–799 (2013).
150. Naas, T. et al. Neonatal infections with multidrug-resistant ESBL-producing *E. cloacae* and *K. pneumoniae* in neonatal units of two different hospitals in Antananarivo, Madagascar. *BMC Infect. Dis.* **16**, 1–10 (2016).
151. Das Choudhury, D. et al. Carbapenem resistant Enterobacteriaceae neonatal gut colonization: a future concern in healthcare settings. *Indian J. Microbiol. Res.* **5**, 348–354 (2018).
152. Leikin-Zach, V. et al. Neonatal risk factors for colonization with extended-spectrum beta-lactamase-producing bacteria in the neonatal intensive care unit. *Isr. Med. Assoc. J.* **20**, 286–290 (2018).

AUTHOR CONTRIBUTIONS

D.D.F. conceptualized the review article, drafted the initial manuscript, and reviewed and revised the manuscript. K.C. conceptualized the review article, contributed to the initial manuscript, and reviewed and revised the manuscript. J.S.G. and K.M.P. conceptualized the review article and reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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The authors declare no competing interests.

ADDITIONAL INFORMATION

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