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

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Abstract

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 *Enterobacteriales* and carbapenem-resistant *Enterobacteriales* (CRE). We include published single center studies, neonatal collaborative reports, and national surveillance data. Risk factors for and mechanisms of resistance are discussed. Additionally, we discuss current recommendations for empiric antibiotic therapy for suspected infections, as well as definitive treatment options for key

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multidrug resistant organisms. Finally, we review best practices for prevention and identify current knowledge gaps and areas for future research.

Keywords

neonatology; infection; prematurity; microbiology; antibiotic resistance

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 (U.S.) 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 prevention of MDR-GN infections as a top pediatric research priority in 2020.(10)

Newborns admitted to the neonatal intensive care unit (NICU), and 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 contemporary epidemiology of neonatal MDR-GN infections in the U.S. 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 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 multidrug resistant 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 U.S. 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 are caused by a variety of other gram-positive and gram-negative bacteria and fungi.(15-17) Among infants with LOI in the U.S., 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 multi-center 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 health care 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 non-chromosomal 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, or the Bush-Jacoby-Medeiros system, which categorizes β -lactamases based on function and susceptibility to β -lactamase inhibitors (Table 1).(28) Regardless of 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.

Non-enzymatic mechanisms of resistance also contribute to extended-spectrum cephalosporin and carbapenem resistance. These generally result in decreased intra-cellular concentrations of antibiotics and include porin mutations and 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 antibiotics, resulting in a multidrug resistant phenotype.(34) AcrAB-TolC is a clinically important efflux pump produced by *Enterobacterales* species resulting in a multidrug resistant phenotype.(35)

Extended spectrum β -lactamases (ESBL)

ESBL genes are most often found in *E. coli*, *K. pneumoniae*, *K. oxytoca*, and *Proteus mirabilis*.(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 the 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 non-susceptibility, defined by the Clinical and Laboratory Standards Institute as a ceftriaxone minimal inhibitory concentration (MIC) of ≥ 2 mcg/uL, 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 non-enzymatic mechanisms of resistance, can also produce a phenotype of ceftriaxone non-susceptibility.(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)

Carbapenem-resistant Enterobacterales (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 mechanism of carbapenem resistance, which can occur by either: 1) production of a carbapenemase, or 2) 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 multi-center 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 U.S.; 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 U.S. 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 U.S. found that one quarter of neonatal gram-negative pathogens were nonsusceptible to 1 commonly used antimicrobials including gentamicin, piperacillin-tazobactam, 3rd and 4th generation cephalosporins, and carbapenems.(63) A report of 721 infants with *E. coli* infection admitted to NICUs from 2009-2017 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 2015-2017 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

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 U.S., rates of neonatal ESBL-producing *Enterobacterales* remain low, and neonatal CRE are rare. In two New York NICUs, less than 1% of admitted infants were colonized with ESBL phenotype bacteria, and a study of four NICUs in the U.S. found that less than 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)

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) *E. coli* and *Klebsiella* species are the most common MDR-GN organisms in both international and U.S. settings. In particular, *K. pneumoniae* is the most frequently identified CRE. *Acinetobacter baumannii*, 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 U.S., 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 of 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 less than 37 weeks and very-low birth weight (<1500 grams) 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 3rd 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 greater contributing factor for risk of resistant infection than the specific antibiotics prescribed.(80)

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 *Enterobacteriales* colonization among mothers and preterm infants.(100) Incidence of ESBL colonization was 6-fold higher among infants born to colonized versus noncolonized mothers.(100) There are case reports of EOI and LOI caused by ESBL-*Enterobacteriales* 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 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 re-colonization 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 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 (EOI)

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 U.S., for 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, 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 U.S., 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 (LOI)

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 an antistaphylococcal penicillin (i.e. nafcillin, oxacillin, flucloxacillin) combined with an aminoglycoside (i.e. gentamicin,

amikacin) or a 3rd 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 3rd generation cephalosporins as 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 a 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 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 extra-corporal therapies.(124) Given these complexities, and 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 non-susceptibility. The highest quality data informing the treatment of ESBL infections comes 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 potential use of piperacillin-tazobactam or cefepime if susceptible for 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 mcg/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 mcg/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 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 post-menstrual age to < 3 months is ongoing (NCT04126031). Clinical data surrounding use of ceftazidime-avibactam in neonates are limited to case reports.(135,136) Meropenem-vaborbactam is also a β -lactam/ β -lactamase inhibitor which 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 birth-18 years old (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 birth through 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 and over in 2020. Pediatric and neonatal data are extremely limited, but the results of pharmacokinetic modeling study presented in abstract form demonstrated that doses of 30 mg/kg 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 is 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 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 decreased in ESBL-producing *K. pneumoniae* colonization.(144) In a neonatal ESBL or CRE outbreak scenario, prompt control with 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 *Enterobacteriales* 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.

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Impact:

- Surveillance and prevention of multidrug resistant gram-negative (MDR-GN) infections is a pediatric research priority
- A rising prevalence of MDR-GN neonatal infections, specifically extended-spectrum β -lactamase (ESBL)-producing *Enterobacterales* and carbapenem-resistant *Enterobacterales* (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

Table 1.

Summary of major extended spectrum β -lactamase and carbapenemase enzymes

Amber 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	Resistant to all cephalosporins and carbapenems (variably elevated meropenem MIC)	AVI, REL, VAB	Global
Class B	Metallo- β -lactamase (MBL)	Zinc	NDM VIM IMP	Resistant to all β -lactams except ceftiderocol; may retain susceptibility to monobactams but co-production of class A ESBLs is common, limiting utility of monobactams unless combined with an active β -lactamase inhibitor	None	Global 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 co-produced and lead to cephalosporin resistance	AVI	Mediterranean basin, Middle east

Abbreviations: 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)

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
<i>International</i>					
Mitra et al(148) (abstract)	2011	England and Wales	Cross-sectional survey on occurrence of ESBL infection	198 units invited to complete survey	<ul style="list-style-type: none"> • 35/133 (26%) units reported ESBL positive results within the 2 years' prior • ESBL-producing <i>E. coli</i> and <i>Klebsiella</i> species were most common
Viswanathan et al(21)	2011	India	MDR-GN organisms causing EOI/LOI	158 infants	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 56% were colonized with ESBL • Multiple colonization found in 27% (11/41)
Benenson et al(144)	2013	Israel	Carriage of ESBL <i>K. pneumoniae</i>	1763 infants	<ul style="list-style-type: none"> • Proportion of neonates acquiring ESBL-producing <i>K. pneumoniae</i> 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 <i>K. pneumoniae</i>	216 infants	<ul style="list-style-type: none"> • 24% colonized were colonized with ESBL-producing <i>K. pneumoniae</i> • 1 infant acquired a clinical infection
Roy et al(149)	2013	India	Susceptibility of <i>K. pneumoniae</i> and <i>E. coli</i> isolates	26 isolates	<ul style="list-style-type: none"> • 60% of <i>K. pneumoniae</i> and 75% of <i>E. coli</i> were ESBL producers
Denkel et al(100)	2014	Germany	Carriage of ESBL	209 VLBW infants	<ul style="list-style-type: none"> • <i>Klebsiella</i> spp. and <i>E. coli</i> were most common • 5.7% were colonized with ESBL
Akturk et al(97)	2016	Turkey	Carriage of CRKP	1671 infants	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 35/39 <i>E. cloacae</i> and 16/20 <i>K. pneumoniae</i> were ESBL-producers
Giuffrè et al(94)	2016	Italy	Carriage of MDR-GN	1152 infants	<ul style="list-style-type: none"> • 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 5-year period
Das Choudhury et al(151)	2018	India	Carriage of CRE (screened on day 0, 3 and 4-10)	300 infants	<ul style="list-style-type: none"> • 8.7% were colonized with CRE • None were colonized on day 0

Author(s)	Publication Year	Region/Country	Focus	Study size	Key Findings
Delhi Neonatal Infection Study collaboration(26)	2016	India	MDR-GN organisms causing EO/LOI	13,530 infants	<ul style="list-style-type: none"> <i>K. pneumoniae</i> was most common <i>Acinetobacter</i> spp were most common GN and 82% were MDR 54% of <i>Klebsiella</i> spp. and 38% of <i>E. coli</i> species were MDR
Turner et al(67)	2016	Cambodia	Carriage of 3rd gen. cephalosporin or carbapenem-resistant organisms	333 infants	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 9.6% were colonized with ESBL <i>K. pneumoniae</i> and <i>E. cloacae</i> were most common
Nour et al(95)	2017	Egypt	Carbapenem susceptibility of GN-LOI	158 infants with GN LOI	<ul style="list-style-type: none"> 37% of GN-LOIs were carbapenem resistant Most common CRE was <i>K. pneumoniae</i>
Singh et al(68)	2018	India	Carriage of CRE	300 infants	<ul style="list-style-type: none"> 8.7% were colonized with CRE <i>K. pneumoniae</i> was most common
Leikin-Zach et al(152)	2018	Israel	Carriage of ESBL	639 infants	<ul style="list-style-type: none"> 13.6% were colonized with ESBL <i>K. pneumoniae</i> was most common
Berberian et al(75)	2019	Argentina	Descriptive report of MDR-GN infections	21 infants	<ul style="list-style-type: none"> Most common pathogens were <i>Acinetobacter baumannii</i> 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	<ul style="list-style-type: none"> <i>K. pneumoniae</i> 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	<ul style="list-style-type: none"> <i>Klebsiella</i> species and <i>E. coli</i> were most common Pooled prevalence of nonsusceptibility for <i>Klebsiella</i> species: gentamicin (66%), ceftriaxone (49%), cefotaxime (78%), amikacin (14%), ESBL (49%-60%), carbapenems (4%) Pooled prevalence of nonsusceptibility for <i>E. coli</i> 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	<ul style="list-style-type: none"> 68% were colonized with ESBL, and 5% were colonized with CRE
Labi et al(90)	2020	Ghana	Carriage of MDR-GN	228 infants	<ul style="list-style-type: none"> <i>Klebsiella</i> species and <i>E. coli</i> were most common

Author(s)	Publication Year	Region/Country	Focus	Study size	Key Findings
Yin et al(84)	2021	China	Carriage of and infection from CRE	1230 infants	<ul style="list-style-type: none"> • Pathogenic GN were cultured in 76.8% of neonates, and half were MDR • 9.2% were colonized with CRE • CRE colonization increased risk of CRE infection
Sands et al(43)	2021	7 LMIC	MDR-GN isolates causing EO/LOI	885 isolates	<ul style="list-style-type: none"> • <i>Klebsiella species</i> and <i>E. coli</i> were most common • GN bacteria were resistant to ampicillin (95%), ceftioaxime (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	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 1% were colonized with third generation cephalosporin resistant GN bacteria
Patel et al(63)	2017	Northeastern U.S.	Susceptibility of GN organisms causing LOI to gentamicin, piperacillin-tazobactam, 3 rd gen. cephalosporins, carbapenems	188 infants	<ul style="list-style-type: none"> • <i>Klebsiella</i> spp. and <i>E. coli</i> were 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
Stoll et al(17)	2020	U.S. (Neonatal Research Network)	Susceptibility of EOI <i>E. coli</i> isolates	86 isolates	<ul style="list-style-type: none"> • 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	U.S. (Premier Health Database)	Susceptibility of <i>E. coli</i> isolated from blood, CSF, or urine	721 infants	<ul style="list-style-type: none"> • 67% nonsusceptible to ampicillin • 17% nonsusceptible to aminoglycosides • 5% with ESBL phenotype • 0% nonsusceptible to carbapenems • 10% of EOI nonsusceptible to ampicillin and gentamicin

Footnotes: Only studies published in 2010 or after were included. Carriage detected by fecal/rectal swabs unless otherwise specified Abbreviations: 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), U.S. (United States); NICU (neonatal intensive

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care unit); CSF (cerebrospinal fluid); VLBW (very-low birth weight); CRE (carbapenem-resistant *Enterobacteriaceae*); CRKP (carbapenem-resistant *Klebsiella pneumoniae*); ESBL (extended-spectrum β -lactamase)

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 grams)	• 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	

Abbreviations: MDR-GN (multidrug resistant gram-negative)