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Antimicrobial Treatment of Serious Gram-Negative Infections in Newborns

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Abstract The choice of antibiotics for serious Gram-negative bacterial infections in the newborn must balance delivery of effective antibiotics to the site(s) of infection with the need to minimize selection of antibiotic resistance. To reduce the risk of selective pressure from large-scale cephalosporin usage, a penicillin–aminoglycoside combination is recommended as empiric therapy for neonatal sepsis. Where Gram-negative sepsis is strongly suspected or proven, a third-generation cephalosporin should ordinarily replace penicillin. Piperacillin-tazobactam can provide better Gram-negative cover than penicillin–aminoglycoside combinations, without the risk of selecting antibiotic resistance seen with cephalosporins, but further clinical studies are required before this approach to empiric therapy can be recommended. For antibiotic-resistant infections, a carbapenem remains the mainstay of treatment. However, rapid emergence and spread of resistance to these antibiotics means that in the future, neonatologists may have to rely on antibiotics such as colistin, whose pharmacokinetics, safety, and clinical efficacy in neonates are not well-defined.

Keywords Neonatal sepsis · Gram-negative bacteria · *Enterobacteriaceae* · *Acinetobacter baumannii* · *Pseudomonas aeruginosa* · Antibiotic resistance · Penicillin · Aminoglycoside · Cephalosporin · Carbapenem · Colistin

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Introduction

Neonates may be infected with a wide range of Gram-negative bacteria. However, the infections that are most common and/or serious, and challenging to treat, are those caused by the family *Enterobacteriaceae* (*E. coli*, *Klebsiella* spp., *Enterobacter* spp., *Serratia* spp., etc.), *Pseudomonas aeruginosa*, and *Acinetobacter baumanii* [1]. Infections are categorized as being early-onset (infections presenting in the first 72 h of life) or late-onset [2••]. The distinction is important because almost all early-onset infections are acquired from the mother, whereas the possible sources (and microbial causes) of late-onset infections are much wider ranging [3•].

Globally increasing antibiotic resistance is seriously limiting antibiotic treatment options, especially for Gram-negative bacterial infections. The risks of antibiotic resistance to nations' security have been recognized and, in 2013, were a focus of discussion at the World Health Assembly [4]. The situation in neonates is particularly perilous. Antibiotic resistance in Gram-negative bacteria causing both early-, and especially late-, onset neonatal sepsis is becoming more common, contributed to by maternal antibiotic exposure during pregnancy [5]; treatment options in this age group are particularly limited, because of lack of clinical experience and limited pharmacokinetic (PK) data for alternative antibiotics; and the control of antibiotic-resistant Gram-negative bacteria in neonatal units (NNUs) is especially challenging [6].

In this article, we will consider the best antimicrobial treatments for serious infections with antibiotic-susceptible and antibiotic-resistant Gram-negative bacteria in newborn babies.

Pharmacological Considerations in Treating Serious Gram-Negative Infections in Newborns

Neonates handle drugs differently from older children and adults, which needs to be considered when prescribing antibiotics for serious sepsis, to ensure dosing that is both clinically effective and safe. There are limited PK data for drugs other than those conventionally used for neonatal sepsis, which presents a particular challenge when prescribing treatment for infections with Gram- negative bacteria that are resistant to standard antibiotic regimens [6]. As well as for antibiotics such as gentamicin, therapeutic drug monitoring can be useful for unfamiliar antibiotics, to ensure that plasma concentrations remain within the therapeutic window.

Routes of Administration

Enteral drug absorption is variable in newborns and may be unavailable in the ill, since the stomach may not always empty effectively. This means that early IV–oral switch therapy (as is advocated for other patients groups) is not usually an option, and most newborns being treated for serious Gram-negative infection will complete their course of therapy with parenteral antibiotics.

Distribution and Elimination

It is important that antibiotics reach the site(s) of suspected infection in adequate concentrations. Good central nervous system (CNS) penetration is often a particularly important consideration in selecting antibiotics for serious neonatal infections, because meningitis is more common in babies than in any other age group, occurring in up to 8 % of cases of sepsis [7]. Whereas adequate concentrations of most β-lactam antibiotics can be achieved in cerebrospinal fluid (CSF), this is not the case of some other antibiotics that are important in treating neonatal Gram-negative sepsis (Table 1) [8, 9].

Neonates have a larger relative total body water and lower body fat, meaning that most antibiotics have a larger volume of distribution and decreased clearance, as compared with older age groups. Most antibiotics used to treat serious Gram-negative infections are excreted in urine. Renal function (glomerular filtration and tubular secretion) is poor at birth, especially in the preterm or sick neonate, but these functions improve with postgestational age and as the patient recovers. The half-life of antibiotics that are excreted in the urine can be greatly prolonged—for example, gentamicin ($t_{½}$ 18 h, as compared with 2 h), but it will shorten both as babies recover from sepsis and as they become older. It is sometimes forgotten that dosage and dose intervals may have to change during a course of treatment in the neonate.

Empirical Antibiotic Treatment for Serious Gram-Negative Infections in Newborns

Standard Antibiotic Treatment

It is rarely possible on presentation to distinguish between neonatal sepsis caused by Gram-negative and Gram-positive bacteria. It is also relevant that most neonates who are commenced on antibiotics for suspected sepsis are never proven to have infection [2••]. The choice of empiric antimicrobial therapy needs to balance the need for broad-spectrum cover with risks of harm to individual babies from antibiotic exposure and the impact of large-scale use of broad-spectrum antibiotics on the microbial ecology of the individual baby and the NNU as a whole [10]. Once Gram-negative sepsis is confirmed, initial antimicrobial therapy may need to be modified to target the specific pathogen. The antimicrobial activities and recommended doses of antibiotics used in treatment of neonatal Gram-negative sepsis are given in Table 2.

There are few good quality comparative trials of empiric antibiotic treatment regimens [12], and choice of antibiotic therapy is often based on local opinion rather than good science. The most commonly used regimens are penicillin, ampicillin, or amoxicillin (or flucloxacillin for late-onset sepsis), plus gentamicin or another aminoglycoside, or a third-generation cephalosporin (such as cefotaxime), which may be combined with ampicillin or amoxicillin where activity against listeria is required [2••, 13]. Note that ceftriaxone is not recommended for treating septic neonates, because precipitation, when used together with calcium, can cause severe reactions and ceftriaxone can displace bilirubin from serum albumin, leading to bilirubin encephalopathy. Ceftazidime is also unsuitable as empiric therapy, because it has much less activity against Gram-positive bacteria. However, ceftazidime is useful in treating confirmed neonatal infections with *Pseudomonas aeruginosa*.

Synergy between penicillins and aminoglycosides in the killing of group B streptococci is well-established [14]. However, there is less certain evidence of synergism between β-lactams and aminoglycosides against Gram-negative bacteria, with the interaction between the two drugs being affected by factors such as bacterial susceptibilities to both agents and relative antibiotic concentrations (which change over time during combination therapy) [15].The best prospects for synergism with aminoglycosides are probably with newer β-lactam drugs, including piperacillin-tazobactam and the third- and fourth-generation cephalosporins [16].

Although the quality of most studies is compromised, there are evidence-based reasons why an aminoglycoside-containing regimen is preferable to a cephalosporin-based regimen. First, antimicrobial susceptibility data indicate that gentamicin-containing antibiotic regimens are more reliable than cefotaxime and amoxicillin. In a study of neonatal

Table 1 Cerebrospinal fluid (CSF) penetration of antibiotic classes active against Gram-negative bacteria

Antibiotic Class	CSF Penetration	Notes
Penicillins	Adequate	High doses can be administered because of low toxicity
β-lactamase inhibitors	Below the concentrations used for *in vitro* susceptibility testing	Limited clinical experience of β-lactam-β-lactamase inhibitor combinations in treating meningitis
Cephalosporins	Variable: generally adequate for third generation cephalosporins	High doses can be administered because of low toxicity
Carbapenems	Adequate	Meropenem is preferred to imipenem with cilastatin for treating meningitis because of lower proconvulsive activity.
Aminoglycosides	Inadequate	
Fluoroquinolones	Good	
Chloramphenicol	Good	Bacteriostatic. Limited clinical experience in treating meningitis due to antibiotic-resistant Gram-negative bacteria.
Colistin	Inadequate	Has been administered via the intraventricular route
Fosfomycin	Good	Limited clinical experience in treating meningitis
Tigecycline	Inadequate	
Trimethoprim ± sulphamethoxazole	Good	Limited clinical experience in treating meningitis

septicaemia in England and Wales, only 28 out of 1,966 (1.4 %) Gram-negative bacteria were resistant to penicillin + gentamicin, whereas 149 out of 1,430 (10.4 %) isolates tested against amoxicillin and cefotaxime were resistant to this combination [17•]. Second, there is reasonable evidence that these in vitro observations translate into clinical evidence for non-inferiority, and even of superiority, of aminoglycoside-containing regimens. Clark et al. [18] found that in a cohort study of 128,914 neonates for patients receiving ampicillin, the concurrent use of cefotaxime during the first 3 days after birth either is a surrogate for an unrecognized factor or is itself associated with an increased risk of death, as compared with the concurrent use of gentamicin. This observation was true across all estimated gestational ages. Another meta-analysis of studies in developing countries concluded that third generations were not superior to penicillin plus gentamicin [13]. Although some smaller studies have suggested that cefotaxime is superior, on detailed analysis it is usually impossible to show that cefotaxime is superior for the subset of neonates with Gram-negative bacteraemia without meningitis [19].

Cephalosporins are notoriously associated with the selection of antibiotic resistances, including extended-spectrum β-lactamase (ESBL)-producing Gram-negative bacteria [20] and MRSA [21]. Use of third-generation cephalosporins in neonates is also a risk factor for candidiasis [18]. Probably the main reason for some neonataologists preferring to use cephalosporins is concern about the adverse effects of aminoglycosides. However, there is little evidence that gentamicin use in neonates is associated with an increased risk of ototoxicity [22, 23], even in babies with 12S rRNA mutations specifically related to aminoglycoside ototoxicity [24]. The incidence of nephrotoxicity is probably also low: A Cochrane review did not identify any nephrotoxicity in neonates [22]. Taking account of all the available evidence, we recommend that, where local antibiotic susceptibilities allow, a combination of a penicillin plus an aminoglycoside as empiric therapy is preferable to the use of third-generation cephalosporins.

The main drawback of gentamicin-containing regimens is that they rely almost entirely on the aminoglycoside component to provide Gram-negative cover [25]. Thus, where Gram-negative bacterial sepsis is strongly suspected or proven, most clinicians prefer to prescribe a second agent with activity against Gram-negative bacteria (usually a third-generation cephalosporin) in place of the penicillin. This is mandatory where Gram-negative bacterial meningitis is suspected, because of the poor CSF penetration of aminoglycosides. Although the idea of intraventricular aminoglycosides appears theoretically attractive, a Cochrane review recommended that this treatment modality should be avoided and, indeed, proposed that further trials of this intervention should be avoided [26]. This was based on the result of one trial that found that in infants with Gram-negative meningitis and ventriculitis, use of intraventricular antibiotics in addition to intravenous antibiotics resulted in a threefold increased relative risk for mortality, as compared with standard treatment with intravenous antibiotics alone.

There is growing interest in the use of piperacillin-tazobactam as an alternative empiric regimen for neonatal sepsis that avoids the risks of aminoglycoside-related toxicity and provides more reliable cover against Gram-negative bacteria (with less risk of selecting resistance) than do cephalosporins. A before and after study comparing piperacilllin-tazobactam with ampicillin and gentamicin found no adverse effect on outcomes and less diaper rash in the piperacillin-tazobactam-treated group [27•]. Piperacillin-tazobactam may be effective against, and less likely to select, stably derepressed AmpC β-lactamase-producing mutants in Gram-negative bacteria, such as *Enterobacter* spp. [28].

Table 2 Antimicrobial activities and recommended doses of antibiotics that may be used for treatment of neonatal Gram-negative sepsis

Agent	Activity against:							Recommended doses[a] (intravenous)		Notes
	Enterobacteriaceae					Multidrug-resistant *Acinetobacter baumannii*	*Pseudomonas aeruginosa*	Age <7 days	Age ≥7 days	
	E. coli	*Klebsiella*	*Enterobacter*	*Serratia*	ESBL producers					
Amoxicillin or ampicillin								Amoxicillin: 50–100 mg/kg 12 hourly Ampicillin: 30–60 mg/kg 12 hourly	Amoxicillin: 50–100 mg/kg 8 hourly Ampicillin: 30–60 mg/kg 6–8 hourly	
Co-amoxiclav								30 mg/kg 12 hourly		
Piperacillin–tazobactam								90 mg/kg 8 hourly		
Cefotaxime								25–50 mg/kg 12 hourly	25–50 mg/kg 6–8 hourly	
Ceftazidime								25–50 mg/kg once daily	25–50 mg/kg 8–12 hourly	
Meropenem								30 mg/kg 12 hourly	30 mg/kg 6–8 hourly	
Aminoglycosides								Gentamicin: 4–5 mg/kg 24–36 hourly Amikacin: 15 mg/kg 24 hourly		TDM[b] required
Ciprofloxacin								10 mg/kg 12 hourly		Consider TDM[b] in serious infections
Colistin								25,000 units/kg 8 hourly		TDM[b] recommended
Fosfomycin								50 mg/kg 12 hourly	100 mg/kg 12 hourly	
Tigecycline								Insufficient data		

Key: >75% of isolates resistant; 25-75% of isolates resistant; >75% of isolates sensitive

[a] Doses based on those recommended in the British National Formulary for Children (BNFC) [11]

[b] Therapeutic drug monitoring

Although, in combination with gentamicin, it has been shown to be effective in treating babies with enterobacter infection [29], there is insufficient evidence to recommend it as monotherapy in this setting. There also remains uncertainty about optimal dosing for neonates: A recent PK study suggested that higher doses and/or more frequent dosing

regimens may be required [30]. Another concern is whether the β-lactamase inhibitor can provide effective protection against β-lactamase enzymes in CSF, although meningitis has been successfully treated in an animal model [31]. At present,– piperacillin-tazobactam is certainly worth considering as an alternative to third-generation cephalosporins in units where aminoglycoside-resistant Gram-negative bacteria are prevalent or where there has been unfavorable experience with cephalosporins.

Treatment of Infections with Antibiotic-Resistant Gram-Negative Bacteria

Background to the Problem of Antibiotic-Resistant Gram-Negative Bacteria in Neonates

Many resistance mechanisms have been identified in Gram-negative bacteria, including enzyme production, overexpression of efflux pumps, porin (and therefore permeability) deficiencies, and target site alterations. Moreover, multiple resistance genes frequently coexist in the same organism, and interstrain, interspecies, and intergenus spread of resistance genes can occur among Gram-negative bacteria. It is now not uncommon for Gram-negative bacteria to be multidrug resistant (nonsusceptible to at least one agent in three or more antibiotic classes) or extensively drug resistant (nonsusceptible to at least one agent in all but one or two antibiotic classes), although pan-drug resistance fortunately remains rare [32].

A multicenter study in Asia showed that 30 % of *Enterobacteriaceae* in NNUs were resistant to both cephalosporins and gentamicin [33]. A systematic review similarly reported that a significant proportion of neonatal bacteraemias in developing countries are not covered by either third-generation cephalosporins or aminoglycosides [34]. While the current position in Europe and North America may be less serious, multidrug- and extensively drug-resistant *Enterobacteriaceae* still appear sporadically and as outbreaks in NNUs. As compared with some other patient groups, resistance to multiple antibiotics in *P. aeruginosa* and *A. baumannii* is uncommon in neonates [35].

Treatment of Infections with Aminoglycoside-Resistant Gram-Negative Bacteria

Aminoglycoside resistance, mediated by enzymic destruction by aminoglycoside-converting enzymes (ACEs) may occur in *Enterobacteriaceae*. Different ACEs have different substrate profiles, meaning that some gentamicin-resistant bacteria remain susceptible to tobramycin or amikacin. Where isolates are pan-aminoglycoside resistant, alternative antibiotics include cefotaxime, piperacillin-tazobactam, and the carbapenems. Piperacillin-tazobactam is best avoided when treating possible or confirmed meningitis, for the reasons discussed earlier.

Treatment of Infections with ESBL-Producing Gram-Negative Bacteria

During the past decade, ESBL-producing Gram-negative bacteria have become one of the most important antibiotic-resistant bacteria [36]. ESBLs confer resistance to penicillins and cephalosporins and often coexist with resistance to other antibiotic classes, including the fluoroquinolones and aminoglycosides. Unlike many other antibiotic-resistant bacteria, ESBL-producing bacteria occur relatively frequently as community-acquired pathogens [37, 38]; this means that newborns are potentially at risk of mother-to-baby transmission of these bacteria, as well as nosocomial acquisition. The carbapenems have become the mainstay of treatment of serious infections with ESBL-producing Gram-negative bacteria. Carbapenems should normally be used as monotherapy, because there is no evidence of benefit from addition of an aminoglycoside, even if the infecting bacterium remains amoniglycoside sensitive. Meropenem is probably the most widely used carbapenem in neonatology, its use being supported by ongoing multinational pharmacokinetic and clinical studies. Imipenem with cilastatin has the drawback of being associated with a higher rate of CNS side effects. Doripenem is a newer carbapenem that has greater activity against *Pseudomonas aeruginosa*; however, there is only limited experience with this agent in neonates [39]. Temocillin is an old β-lactam antibiotic that has been little used in most countries in the past because of its limited spectrum of activity (inactive against Gram-positive bacteria, anaerobes, and *P. aeruginosa*). However, it is resistant to most Gram-negative beta-lactamases, making it a candidate for treatment of confirmed infections with ESBL-producing bacteria [40]. There is, however, little experience of using this drug in neonates.

Treatment of Infections with Carbapenem-Resistant Gram-Negative Bacteria

Enterobacteriaceae that are nonsusceptible to carbapenems are also increasingly being encountered and, like ESBL-producers, seem to be emerging in the community, as well as in hospitals [41]. Again, nonsusceptibility to carbapenems frequently coexists with resistance to other antibiotic classes, including the aminoglycosides and fluoroquinolones, leaving very limited therapeutic options for infections with these bacteria [42]. Resistance can be due to the production of carbapenemase enzymes, or lower-level resistance can be associated with other mechanisms such as decreased permeability of the outer membrane or efflux mechanisms. In *A. baumannii* discordant resistance to carbapenems (for

example, susceptibility to imipenem but resistance to meropenem and doripenem) may be mediated by naturally occurring carbapenemases [43, 44]. Thus, for this species at least, it may be worthwhile undertaking in vitro susceptibility testing for all carbapenems when a resistant strain is encountered.

The optimal treatment for infections caused by carbapenem-resistant Gram-negative bacteria is not established, and it is recommended that treatment should be planned in conjunction with a clinical microbiologist or infectious disease specialist [45]. For the few infections with isolates that remain aminoglycoside or fluoroquinolone susceptible, treatment with these agents may be possible. There is reasonable clinical experience, and evidence of the safety, of using ciprofloxacin in neonates, although it is based mainly on case reports rather than systematic studies [46]. Ciprofloxacin has the advantage that it offers good CNS penetration.

For lower-level carbapenem-resistant infections, higher doses and/or continuous infusions of carbapenems [47], combined with an aminglycoside to which the infecting bacterium is susceptible, have been used. However, there have been no trials to confirm the validity of this treatment approach. For high-level carbapenem resistance in extensively drug-resistant bacteria, use of colistin must be considered.

There is considerable experience of using colistin in neonates, but it must be noted that colistin is inactive against *Proteus* spp. and *Serratia* spp. Doses ranging from 40,000 to 225,000 IU/kg/day have been used. To reduce the risk of underdosing, we recommend commencing colistin at a dose of at least 75,000 IU/kg/day and monitoring plasma concentrations, aiming for a peak plasma concentration of 10–15 mg/l. There is increasing confidence that colistin is safe, even when given at higher doses, for prolonged periods, and in combination with other nephrotoxic drugs [48]. In adults, colistin as monotherapy has been reported to be inferior to combination therapy [45], suggesting that it is advisable to use it, where possible, in conjunction with a second drug, such as an aminoglycoside. In vitro, there may be synergy between colistin and carbapenems, especially against *A. baumannii*, but the clinical relevance of this is unclear [49]. Aerosolized colistin has been suggested as an adjunctive therapy for pneumonia with multiple antibiotic-resistant Gram-negative bacteria, especially *P. aeruginosa* and *A. baumannii* [50]. CSF penetration of colistin is poor (5 % of serum concentration) [51], and administration of intraventricular colistin may have to be considered [52], especially where there are no options to co-prescribe a systemic agent that does penetrate CSF well.

Other last-resort treatments for extensively drug-resistant Gram-negative bacterial infections include chloramphenicol and trimethorpim or co-trimoxazole. However, co-resistance to these agents is common in Gram-negative bacteria that produce ESBLs or carbapenemases [53], and there is little or no evidence for the efficacy of these agents in treating serious neonatal infections. Fosfomycin is a phosphonic acid derivative that has broad-spectrum bactericidal activity, including against extensively drug-resistant *Enterobacteriaceae*, *A. baumannii*, and *P. aeruginosa*. Other desirable characteristics it displays are excellent tissue and fluid penetration, in-vitro synergism with other classes of antibiotics, and low toxicity. One of the concerns about using fosfomycin is the potential for mutational resistance developing during treatment, although at least when treating simple infections, this occurs less frequently than it does in vitro [54]. Use in combination with other antibiotic classes can further limit the chance of developing resistance. Unfortunately, there is relatively little experience of using fosfomycin in neonates [55•], but it is certainly a candidate as a component of last-resort treatments for extensively drug-resistant Gram-negative bacteria.

Tigecycline is active against many multidrug-resistant Gram-positive and Gram–negative bacteria, but not against *P. aeruginosa*. It is probably ineffective for intracranial infections [56]. As a tetracycline analogue, it is likely that tigecycline could inhibit bone growth in children and cause dental staining. Therefore, use in neonates can be justified only as a final-resort salvage therapy [57].

Duration of Treatment

There are no comparative trials to determine the optimal duration of treatment for serious neonatal infections. As a result, there is a tendency to err on the side of safety and treat babies for longer than may be necessary. Overlong treatment courses are not without risk (e.g., selection of antibiotic resistance, secondary bacterial or fungal infections, increased central venous catheter days, increased length of stay). For neonates without meningitis or another deep-seated focus of infection, 7 days of treatment will usually suffice, provided that the baby has fully recovered. For babies with more complex infections, treatment for at least 21 days is recommended [2••].

In the absence of an evidence-based strategy for treating multidrug- and extensively drug-resistant Gram-negative bacterial infections, repeat cultures to monitor the microbiological response to treatment should be considered.

Future Prospects for Treating Infections with Antibiotic-Resistant Gram-Negative Bacteria

The pharmaceutical industry is now being incentivized to identify new antimicrobial agents that are active against Gram-negative bacteria. We are some way from any truly novel antimicrobials being licensed and marketed. However, a variety of new agents that promise to be of some value in

treating infections with multidrug- and extensively drug-resistant Gram-negative bacteria are under development, with some of these in phase II clinical trials [58•]. Of course these agents are likely to be licensed first for use in adults, and there will be few data to support their use in newborns.

Conclusions

The rapid globalization of multidrug- and extensively drug-resistant Gram-negative bacteria is already seriously challenging antibiotic treatment options for neonates with Gram-negative bacterial infections. It will be some years before any new treatment options for neonates become available. Until then, we must strike a balance between avoiding overusing antibiotics and ensuring that appropriate treatment is not withheld from babies who do have infection. A combination of a penicillin and an aminoglycoside is recommended as the most appropriate empiric treatment for neonatal sepsis in most cases but may need to be modified if Gram-negative infection is confirmed. The carbapenems are the mainstay of treatment for most infections with multidrug-resistant bacteria in Western countries, but we increasingly have to consider using drugs for which there is only limited neonatal experience.

Compliance with Ethics Guidelines

Conflict of Interest James Gray has no conflicts of interest. Hirminder Ubhi has no conflicts of interest. Philip Milner has no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the authors.

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- • Of importance
- •• Of major importance

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