Published in final edited form as:

Expert Rev Clin Pharmacol. 2014 May ; 7(3): 327–340. doi:10.1586/17512433.2014.909281.

Pharmacokinetics and safety of recently approved drugs used to treat methicillin-resistant *Staphylococcus aureus* infections in infants, children, and adults

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Summary

Methicillin-resistant *Staphylococcus aureus* (MRSA) remains a significant cause of morbidity in hospitalized infants. Over the past 15 years, several drugs have been approved for the treatment of *S. aureus* infections in adults (linezolid, quinupristin/dalfopristin, daptomycin, telavancin, tigecycline, and ceftaroline). The use of there majority of these drugs has extended into the treatment of MRSA infections in infants, frequently with minimal safety or dosing information. Only linezolid is approved for use in infants, and pharmacokinetic data in infants are limited to linezolid and daptomycin. Pediatric trials are underway for ceftaroline, telavancin, and daptomycin; however, none of these studies includes infants. Here, we review current pharmacokinetic, safety, and efficacy data of these drugs with a specific focus in infants.

Keywords

linezolid; daptomycin; quinupristin; dalfopristin; ceftaroline; tigecycline; neonate; sepsis

Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) infections are common and are associated with increased mortality, morbidities, and healthcare costs [1,2]. In 2012, in the United States, there were an estimated 80,461 cases of invasive MRSA infections [3]. A retrospective analysis of 25 children's hospitals reported that the incidence of MRSA infections increased 10-fold between 1999 and 2008 (2 cases vs. 21 cases per 1000, P<0.001) [4]. Furthermore, the proportion of staphylococcal infections due to MRSA in children's hospitals in the United States doubled in the same time period (15% vs. 36%) [4]. In 2010, invasive MRSA infection incidence was higher in infants <90 days of age

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compared with older infants and children— 4 times higher in this population than in infants aged 3–11 months and more than 40 times higher than in children aged 11–17 years [5].

Given the increase in MRSA infections over the last decade, the percentage of hospitalized children with *S. aureus* infection that received anti-MRSA antibiotics increased between 1999 and 2008 (52% vs. 79%), while the percentage of hospitalized children receiving beta-lactam drugs decreased (66% vs. 30%, P<0.001) [4]. During this time period, the percentage of hospitalized children with *S. aureus* infection given clindamycin and linezolid increased (clindamycin, 21% vs. 63%; linezolid, 0% vs. 5%) while vancomycin use remained stable (36% vs. 37%) [4].

Current treatment options for infants with MRSA infection based on the clinical practice guidelines by the Infectious Diseases Society of America vary depending on the site of infection [6]. First-line treatment is with intravenous (IV) vancomycin for severe manifestations of MRSA infection [6]. Alternative antibiotic treatment includes clindamycin, linezolid, daptomycin, quinupristin/dalfopristin, rifampin, telavancin, or trimethoprimsulfamethoxazole [6].

The objective of this report is to review available pharmacokinetic (PK), safety, and efficacy data of recently approved antibiotics for MRSA infection in infants. Our focus was to describe data pertaining to the infant population, though all age groups are briefly discussed. Clinical trials in infants are needed because the PK, efficacy, and safety of drugs may be significantly different from that observed in adults. Maturation in drug elimination pathways and differences in body composition affect drug disposition, often necessitating age- or weight-based dosing recommendations [7]. In addition, exposure-response relationships are also needed to characterize developmental factors that affect drug action. The disease process of MRSA infection in infants can reasonably be assumed to be similar to adults, and if the exposure-response relationship is reasonably assumed to be the same in infants and adults, the Food and Drug Administration (FDA) only requires PK and safety studies for drug labeling changes in the pediatric population.

Methods

We conducted searches for each drug using the PubMed database and the following medical subject heading (MeSH) and title/abstract [tiab] terms: pharmacokinetics [MeSH], pharmacokinetics [subheading], safety [tiab], efficacy [tiab], and the drug name [tiab]. We also retrieved drug labels from the FDA registry [201]. We included all drugs approved in the last 15 years for use against staphylococcal infections (linezolid, daptomycin, quinupristindalfopristin, telavancin, tigecycline, and ceftaroline) (Table 1). There were no exclusion criteria in our search strategy. All articles regarding PK, safety, and efficacy in infants were included. Articles representative of PK, safety, and efficacy in children and adults were included at the authors' discretion.

Linezolid

Linezolid is a synthetic oxazolidinone that binds to the bacterial 50S ribosomal subunit preventing the formation of the 70S initiation complex and stopping the initiation of

translation [8,9,101]. Linezolid is primarily bacteriostatic against enterococci and staphylococci isolates and bactericidal against the majority of streptococci isolates [101]. The drug is highly effective against gram-positive bacteria and has been found in vitro to have 90% minimum inhibitory concentration values (MIC_{90}) of 1, 2, and 4 μg/mL against streptococci, enterococci, and staphylococci, respectively [10].

Pharmacokinetics of Linezolid

Linezolid is given either orally or as an IV infusion at a dose of 600 mg in adults [101]. Linezolid is extensively absorbed following oral dosing with a bioavailability of 100% [11]. Linezolid follows a linear PK elimination profile after either single or multiple dose administration. In adults, the time at maximum concentration (T_{max}) of the drug is 0.5 hours following a 600 mg IV dose. The volume of distribution (V_d) of linezolid is 0.65 L/kg, and it is 31% bound to plasma proteins [101]. The systemic clearance (CL) of linezolid is 8.3 L/h [12,13,101]. Linezolid is primarily excreted renally; over 35% of the drug is excreted as the parent drug in urine, and an additional 50% is excreted as metabolites in urine [14,15]. The elimination half-life ($T_{1/2}$) of the drug in adults is approximately 4.9 hours (Table 2) [13,101].

The majority of the linezolid PK data in children comes from 4 trials evaluating 182 children aged 0–18 years, of whom 41 were <3 months of age [101]. Linezolid was given as a 10 mg/kg IV infusion in subjects <11 years and as a 600 mg IV infusion in subjects aged 12–18 years [101]. The CL of linezolid varied significantly as a function of the postnatal age and gestational age of the infant at birth. The mean CL in premature infants <1 week of age was 0.12 L/kg/h compared with 0.23 L/kg/h for term infants <1 week of age [16]. Following the first week of life, linezolid body weight-normalized CL in infants increased to 0.31 L/kg/h, approximately 3 times that of the adult estimate (0.1 L/kg/h). Linezolid weight-normalized CL remained elevated for the first 3 months of life and reached adult values by adolescence (Table 2) [16,101].

Safety and Efficacy of Linezolid

The safety and efficacy of linezolid in adults have been evaluated in a number of large clinical trials. For adults treated with 400 mg of linezolid every 12 hours for skin and skin structure infections (n=548), 25% suffered at least 1 drug-related adverse event [101]. The most common of these reactions were diarrhea (5%), nausea (3%), and headache (3%). These events were comparable to the comparator, clarithromycin, with which subjects also reported diarrhea (5%), nausea (3%), and headache (2%). The discontinuation rate for linezolid due to drug-related adverse events was also similar to clarithromycin (3.5% vs. 2.4%, respectively) [101].

A separate study in adults (n=66) compared the efficacy of linezolid versus vancomycin for the treatment of MRSA skin and skin structure infection. Subjects were either given linezolid 600 mg every 12 hours or vancomycin 1 g every 12 hours. Clinical efficacy as measured by cure rate in microbiologically evaluable subjects was higher in subjects treated with linezolid than in subjects treated with vancomycin (79% vs. 73%) [101].

The safety and efficacy of linezolid in pediatric subjects has been evaluated in 2 phase 3 comparator-controlled clinical trials [17,18,101]. The first study examined the safety and efficacy of linezolid versus vancomycin for the treatment of known or suspected antibiotic-resistant, gram-positive infection [18]. In the first study (n=321, ages 0–11 years), 219 subjects (median age 1.5 years) were given IV linezolid (10 mg/kg every 8 hours), while 102 subjects (median age 1.8 years) received IV vancomycin (10–15 mg/kg every 8 hours) [18]. Drug-related adverse events were more frequent in the vancomycin-treated group than in the linezolid-treated group (34% vs. 19%, P=0.003) [18]. Discontinuation due to drug-related adverse events was also higher in the vancomycin- treated group (6% vs. 1%, P=0.008) [18]. The most common adverse event seen in linezolid-treated subjects was diarrhea (4%). Efficacy of linezolid as measured by overall cure rate in clinically evaluable subjects was similar to vancomycin-treated subjects (89% vs. 84%, P=0.31) [18].

The second study (n=508) examined the safety and efficacy of linezolid for the treatment of skin and skin structure infections in children [17]. Dosing of subjects in the trial varied based on age. Linezolid was given as an oral suspension to 146 subjects aged 5–11 years (10 mg/kg every 12 hours) and 102 subjects aged 12–17 years (600 mg every 12 hours). Adverse events occurring in >5% of linezolid-treated subjects included diarrhea (8%) and headache (6%), which were similar to the rates seen in children receiving the comparator, cefadroxil (8% and 4%, respectively). A trend towards lower discontinuation due to adverse events was observed for the linezolid-treated group (2% vs. 4%), but this difference was not found to be statistically significant [17]. One serious drug-related adverse event was reported in a subject treated with linezolid who had a highly elevated lipase level that returned to normal after 3 days [17].

The safety of linezolid in infants was evaluated in a phase 3 study (n=63), which examined the safety and efficacy of linezolid versus vancomycin for the treatment of known or suspected antibiotic-resistant, gram-positive infection [19]. Forty-three children and 20 infants were either given IV linezolid 10 mg/kg every 8 hours or IV vancomycin 10–15 mg/kg every 6–24 hours. Drug-related adverse events occurred more frequently in subjects treated with vancomycin than in those treated with linezolid (32% vs. 12%, P=0.06). Adverse events that occurred more commonly in subjects treated with linezolid included: thrombocytopenia (5%), candidiasis (2%), hyperglycemia (2%), and anemia (2%). The efficacy of linezolid in clinically evaluable subjects successfully treated for bacteremia was similar to those treated with vancomycin (84% vs. 77%, P=0.55) [19].

Daptomycin

Daptomycin is the first drug in the lipopeptide class of antimicrobials. It is derived from a fermentation product of *Streptomyces roseosporus* [102]. Daptomycin forms channels through which K^+ moves out of the cell, causing a change in the membrane potential [20]. The change in membrane potential results in inhibition of DNA, RNA, and protein synthesis in the bacterium [102]. This mechanism of action allows the drug to have bactericidal activity against multiple strains of gram-positive, antibiotic-resistant bacterium [21]. Daptomycin has been found in vitro to have an MIC_{90} of 0.5 μg/mL, 0.5 μg/mL, and 2–4 μg/mL against staphylococci, streptococci, and enterococci, respectively [21,22].

Pharmacokinetics of Daptomycin

Daptomycin is given in adults as an IV infusion at a dose of 4 mg/kg every 24 hours [102]. In healthy adults, daptomycin has linear PK following single or multiple doses up to 8 mg/kg. Daptomycin distributes primarily into extracellular fluid (V_d of 0.1 L/kg) and is 87–93% reversibly bound to plasma proteins [23,102]. The CL of the drug in healthy adults is 0.011 L/kg/h [102]. Daptomycin is renally excreted, and dosing must be adjusted for adult subjects who have impaired creatinine clearance or who are undergoing dialysis [24]. Daptomycin has a $T_{1/2}$ of 8–9 hours (Table 2) [20,24–27].

At doses of 4 mg/kg every 24 hours in children 12–17 years of age, the area under the concentration curve (AUC) of daptomycin approximated adult values shown to be therapeutically effective (375 μg/mL*h vs. 414–494 μg/mL*h, respectively) [26–28,102]. However, for children aged 2–12 years who were given 4 mg/kg every 24 hours, the exposure to daptomycin (AUC) was lower than in adults (215–271 μg/mL*h vs. 414–494 μg/mL*h, respectively) [26–28,102]. Larger weight-based doses or more frequent dosing of daptomycin is required in children <12 years of age to match adult AUC values [28].

In a study of a single 6 mg/kg dose of daptomycin in 20 infants (median gestational age 32 weeks; range 23–40 weeks), the median exposure from 0–24 hours (AUC_{0-24}) of the drug in infants was significantly lower than that reached in adults (262 μg/mL*h vs. 414–494 μg/mL*h) [26,27,29]. This was due to the increased body weight-normalized CL of the drug in infants (0.02 L/kg/h) compared with adults (0.01 L/kg/h) [25,29]. The investigators concluded that higher doses of daptomycin were needed for treatment of infection in infants [29]. A case series examined the PK of daptomycin given at higher daily doses (6 mg/kg every 12 hours) in 2 infants (gestational age 23 weeks and 32 weeks) at postnatal ages of 31 weeks and 35 weeks, respectively [30]. This increased dosing regimen of 6 mg/kg every 12 hours led to peak and trough values (C_{max}, C_{min}) of the drug in infant 1 (41.7mg/L, 12.7mg/L) and infant 2 (36.7mg/L, 16.3mg/L) that closely approximated the clinically effective levels in adults (58mg/L, 7mg/L) treated with daptomycin (4 mg every 24 hours) (Table 2) [30].

Safety and Efficacy of Daptomycin

A phase 3 study in adults (n=558) compared daptomycin against comparator treatment (IV cloxacillin, nafcillin, oxacillin, flucloxacillin 4–12 g every 12 hours or vancomycin 1 g every 12 hours) for complicated skin and skin structure infection. Eighteen percent of adults given daptomycin 4 mg/kg daily suffered at least 1 drug-related adverse event [31]. Adverse events reported in >5% of subjects included: constipation (6%), nausea (6%), injection site reaction (6%), headache (5%), and diarrhea (5%). Severe adverse events were observed in 11% of subjects given daptomycin vs. 9% of subjects given comparator medications [31]. The only severe adverse event to occur more often in daptomycin-treated subjects than in comparator-treated subjects was cellulitis (1% vs. 0%). For the treatment of complicated skin and skin structure infections, the clinical success rate of daptomycin was similar to the clinical success rate seen for other comparator antimicrobials (83% vs. 84%, respectively) [31].

In another phase 3 study (n=120), daptomycin (6 mg/kg every 24 hours) was evaluated versus comparator medications (IV nafcillin, oxacillin or flucloxacillin 2 g every 4 hours or vancomycin 1 g every 12 hours) for the treatment of bacteremia and endocarditis in adults [32]. Thirty-five percent of subjects suffered at least 1 drug-related adverse event, of which 8% were severe enough to warrant daptomycin treatment discontinuation. Adverse events observed in >5% of daptomycin-treated subjects included: anemia, diarrhea, vomiting constipation, nausea, hypokalemia, renal impairment, headache, and peripheral edema. Creatinine kinase (CK) levels were elevated in 25% of subjects treated with daptomycin, and 2.5% of subjects discontinued treatment due to elevated CK levels. For the treatment of bacteremia and endocarditis, the clinical success rate of daptomycin was comparable to standard therapy with gentamicin and an anti-staphylococcal penicillin or vancomycin (45% vs. 42%, respectively) [32].

In clinical practice, daptomycin is recommended at doses that are higher than approved (4–6 mg/kg) [6]. In small clinical studies, doses up to 12 mg/kg every 24 hours have been tolerated with no serious adverse events or treatment discontinuations noted [25].

Daptomycin is not indicated for use in the pediatric population, but its use has been evaluated in several studies [102]. A study of 16 children with a median age of 6.5 years evaluated use of daptomycin (4 mg/kg every 24 hours) in subjects with persistent bacteremia or failing conventional antimicrobial therapy [33]. Bacteremia resolved within 72 hours in 6 of 7 subjects with prior positive blood cultures. No adverse drug events were observed during daptomycin treatment [33]. A second study of daptomycin in which subjects aged 2–17 years old (n=22) were given 4 mg/kg every 24 hours found that only 1 subject had an adverse drug event (infusion site reaction), and no subjects withdrew from the study [28]. None of the 22 child subjects treated had elevations in CK values during treatment [28]. There are limited published data regarding the safety and efficacy of daptomycin in infants. In a study of 20 infants with a median age of 32 weeks gestation (range 23–40 weeks), a single dose of daptomycin (6 mg/kg) was administered, and there was no observed elevation in CK levels or adverse drug events [29]. In a small report (n=3) of daptomycin use (6 mg/kg every 12 hours) in severely ill infants, no adverse drug events or elevated CK values were recorded [34]. Treatment with daptomycin resulted in negative blood cultures at a dose of 6 mg/kg every 12 hours in 2 subjects after 4 days and at a dose of 15 mg/kg every 12 hours in the third subject after 5 days [34]. A separate report (n=2) evaluated daptomycin (6 mg/kg every 12 hours) in severely ill preterm infants; no adverse drug event was observed in either subject [30].

Ongoing Pediatric Research for Daptomycin

Four phase 1 studies for daptomycin have been completed in the pediatric population: 1) in infants; 2) in children aged 3–24 months; 3) in children aged 2–6 years; and 4) in children aged 2–17 years. Currently, there are 3 daptomycin trials that are recruiting pediatric patients: 1) for treatment of children with bacterial meningitis; 2) a phase 1 study in children with renal disease; and 3) a phase 4 comparative study versus vancomycin or clindamycin for treatment of children with *S. aureus* bacteremia [202].

Quinupristin/Dalfopristin

Quinupristin/dalfopristin is the first of the injectable semisynthetic streptogramin antibacterial agents, comprising quinupristin and dalfopristin in a 30:70 ratio [103]. The drug has a unique mechanism of action that inhibits bacterial protein synthesis by each molecule binding to different sites on the 50s subunit of the ribosome. When combined, they are synergistic as binding of dalfopristin induces a conformational change in the 50s subunit that increases the binding affinity of quinupristin [35]. The combination of both drugs has bactericidal activity against gram-positive pathogens [35]. Quinupristin/dalfopristin has been found in vitro to have an MIC_{90} of 0.25–1 μg/mL, 0.25–1 μg/mL, and 2.0–8.0 μg/mL against staphylococci, streptococci, and enterococci, respectively [103].

Pharmacokinetics of Quinupristin/Dalfopristin

Quinupristin/dalfopristin is administered as an IV infusion at a dosage of 7.5 mg/kg every 12 hours in adults [103]. For the treatment of vancomycin-resistant *Enterococcus faecium* bacteremia, the drug is dosed 7.5 mg/kg every 8 hours [103]. Quinupristin has been found in adults to have a V_d of 0.45 L/kg, while dalfopristin has a V_d of 0.24 L/kg. The CL of quinupristin and dalfopristin are 0.72 L/kg/h [103]. In healthy adults, quinupristin/dalfopristin has biphasic elimination following single or multiple doses. The drug is primarily eliminated hepatically, with 75% and 78% of quinupristin and dalfopristin, respectively, being excreted in bile and recovered in feces as unchanged drug and active metabolites [36,37,103]. Fifteen percent of quinupristin and 19% of dalfopristin are excreted through the urine as unchanged drug and active metabolites [36,37,103]. Quinupristin and dalfopristin's $T_{1/2}$ are 0.85–1.26 hours and 0.70–1.15 hours, respectively (Table 2) [38–41]. We were not able to identify any published PK studies of quinupristin/dalfopristin in children and infants.

Safety and Efficacy of Quinupristin/Dalfopristin

Two phase 3 comparative trials of quinupristin/dalfopristin have been conducted for the treatment of complicated skin and skin structure infection in adults (n=893) [42]. Subjects were either given quinupristin/dalfopristin (7.5 mg/kg every 12 hours) or a comparator medication (IV cefazolin 1 g every 8 hours, oxacillin 2 g every 6 hours, or vancomycin 1 g every 12 hours). In these studies, quinupristin/dalfopristin-treated subjects experienced more non-venous, drug-related adverse events than subjects treated with comparator medication (21% vs. 13%, P<0.001) [42]. In subjects treated with quinupristin/dalfopristin, only nausea was reported in >5% of subjects (6% vs. 2% for comparator, P=0.002). Adverse venous events, most commonly injection site pain and inflammation, occurred more often in subjects treated with quinupristin/dalfopristin than in those treated with comparator medication (66% vs. 28%, P<0.001) [42]. Discontinuation due to an adverse event occurred more often in the quinupristin/dalfopristin group than in the comparator group (19% vs. 5%). However, discontinuation due to treatment failure occurred more often in the comparator group than in the quinupristin/dalfopristin group (11% vs. 5%). The clinical success rate of quinupristin/dalfopristin for the treatment of skin and skin structure infections was similar to treatment with comparator medications (68% vs. 71%, respectively) [42].

In non-comparator studies (n=972), major adverse events possibly related to quinupristin/dalfopristin administration included severe arthralgia and myalgia, each of which occurred in 3% of subjects [103]. A second study examining the efficacy and safety of quinupristin/dalfopristin for the treatment of vancomycin-resistant *E. faecium* infection (n=396) reported higher rates of arthralgia (9%) and myalgia (7%) [43].

Limited studies have evaluated the safety and efficacy of quinupristin/dalfopristin in children. The drug is not labeled for use in infants or children [44]. A retrospective study examined the safety and efficacy of quinupristin/dalfopristin dosed at 7.5 mg/kg every 8 hours in children (n=127) <18 years of age with a confirmed gram-positive bacterial infection that was resistant to conventional treatment [44]. Multiple clinical syndromes were treated, including bacteremia of unknown source, intra-abdominal infection, catheter-related infection, skin and skin structure infection, urinary tract infection, bone and joint infection, respiratory tract infection, and endocarditis. The mean age of subjects was 7.3 years (range 0.1–17.8). Pathogens included vancomycin-resistant *E. faecium* (80%), *Enterococcus* spp. (7%), MRSA (6%), and *S. epidermidis* (4%). Successful clinical response to quinupristin/dalfopristin treatment was demonstrated in 69% of subjects and was similar across all age groups; the microbiological response rate was 78% [44]. The clinical response rates are similar to the response rates that are seen in the adult population (68%) [42,45]. The drug was well tolerated in this population, with only 3% of subjects receiving the drug through a central venous catheter experiencing a venous adverse event. Eight percent of subjects experienced non-venous adverse events, the most frequent being pain (2%) and maculopapular rash (2%) [44]. Significant elevations in aspartate aminotransferase values were observed in 44% of subjects, with 7% of subjects having levels >5 times the upper limit of normal. Furthermore, 42% of subjects experienced elevated levels of bilirubin; 25% of subjects had a bilirubin level >5 times the upper limit of normal during the course of treatment [44].

A prospective, observational, safety and efficacy study of quinupristin/dalfopristin in infants and children (n=19) being treated for glycopeptide-resistant *E. faecium* (GREF) infection post liver transplant reported promising results [46]. Subjects had a median age of 1.5 years (range 0.1–16) and were given quinupristin/dalfopristin (7.5 mg/kg) by slow infusion through a central venous catheter every 8–12 hours. GREF infection was defined as clinical criteria for infection accompanied by isolation of GREF from blood culture, intravascular device tips, or repeated isolation from urine [46]. Complete resolution of GREF infection was reported in 74% of subjects with resolution of fever/leukocytosis and negative cultures. Sixteen percent of subjects had a partial response with negative cultures but recurrence of fever upon treatment discontinuation. Ten percent of subjects had negative cultures but no clinical improvement. Adverse events included elevated alkaline phosphatase in 4 subjects that returned to normal following treatment completion. No arthralgia or myalgia was reported, as subjects in this study were too young or too critically ill to report these adverse reactions [46]. The authors concluded that the drug could be safely administered, with minimal side effects, to critically ill pediatric subjects [46].

Ongoing Pediatric Research for Quinupristin/Dalfopristin

There are currently no active, completed, or open trials for quinupristin/dalfopristin in the pediatric population [202].

Telavancin

Telavancin is a lipoglycopeptide antibacterial agent that is a synthetic derivative of vancomycin [47]. Telavancin has bacteriostatic activity against gram-positive organisms as the drug inhibits cell wall biosynthesis by binding to late-stage peptidoglycan precursors, thereby inhibiting peptidoglycan polymerization and subsequent cross-linking [47,48]. Moreover, telavancin was also found to have bactericidal activity against gram-positive organisms as the drug is also able to disrupt the bacterial cell membrane, causing cell membrane potential depolarization [48,49]. Telavancin has been found in vitro to have MIC_{90} values of 0.5 μg/mL, 0.03–0.06 μg/mL, and 16 μg/mL against MRSA, streptococci, and vancomycin-resistant enterococci, respectively [50,51].

Pharmacokinetics of Telavancin

Telavancin is given as an IV infusion at a dose of 10 mg/kg every 24 hours in adults [104]. The PK of the drug following single and multiple dosing has been well studied in the adult population [52–54]. Telavancin exhibits linear PK in adults over the dose range of 7.5–15 mg/kg every 24 hours [54]. The steady state V_d of telavancin is 0.1–0.15 L/kg, and it is 90–93% bound to plasma proteins, primarily serum albumin [47,54,104]. $T_{1/2}$ of the drug in adults is approximately 6–8 hours [54,104]. The estimated CL of telavancin is 0.012–0.014 L/kg/h (Table 2) [54,104]. Telavancin is primarily excreted renally, with over two thirds of the drug being excreted unchanged in the urine [54]. The PK of telavancin has not been studied in children or infants.

Safety and Efficacy of Telavancin

The safety and efficacy of telavancin in adults have been evaluated in 3 large clinical studies [55]. The drug has not been evaluated in the pediatric population. One study in adults (n=195) with complicated skin and skin structure infections compared telavancin 10 mg/kg every 24 hours against vancomycin 1 g every 12 hours or nafcillin/oxacillin 2 g every 6 hours [55]. A similar percentage of subjects given telavancin or a comparator medication experienced at least 1 adverse event (56% vs. 57%, P≥0.99). In patients taking telavancin, adverse events that occurred in >5% of subjects and at a higher rate than in the comparator group included: nausea (16% vs. 6%, P=0.04), taste disturbance (14% vs. 0%, P<0.01), and insomnia (13% vs. 3%, P=0.02). Serious adverse events occurred more often in subjects treated with telavancin than in the comparator group (7 subjects vs. 3 subjects). The discontinuation rate for telavancin due to adverse events was higher but not statistically different from the comparator treatment (6% vs. 3%). Clinically evaluable cure rates for telavancin were similar to comparator medication for the treatment of complicated skin and skin structure infection (96% vs. 94%, P=0.53) [55].

A second study in adults (n=1867) with complicated skin and skin structure infection compared telavancin versus vancomycin therapy [56,57]. Subjects were either given

telavancin at a dose of 10 mg/kg every 24 hours or vancomycin 1 g every 12 hours. At least 1 adverse event occurred more often in telavancin-treated subjects than in subjects treated with vancomycin (79% vs. 72%) [56,57]. Serious adverse events occurred more frequently in the telavancin-treated group than in the vancomycin-treated group (7% vs. 4%). Discontinuation rates were also higher in the telavancin-treated group (8% vs. 6%) [56,57]. Adverse events among subjects taking telavancin that occurred in >5% of subjects and at a higher rate than in the comparator group included taste disturbance (33% vs. 7%), nausea (27% vs. 15%), and vomiting (14% vs. 7%) [56,57]. The clinical cure rate among subjects with MRSA isolated at baseline was higher in subjects treated with telavancin than in subjects treated with vancomycin (89% vs. 85%) [56].

A third comparator study in adults (n=1503) examined the safety and efficacy of telavancin versus vancomycin for the treatment of hospital-acquired pneumonia caused by gram-positive organisms [58]. Adverse events occurred equally in both telavancin-treated subjects and vancomycin-treated subjects (82% vs. 82%). Telavancin-treated subjects experienced more serious adverse events than vancomycin-treated subjects (31% vs. 26%). Treatment discontinuation was higher among telavancin-treated subjects (8% vs. 5%). Cure rates among telavancin-treated subjects were non-inferior to cure rates among vancomycin-treated subjects for pneumonia caused by all *S. aureus* (78% vs. 75%) and for pneumonia caused by MRSA (75% vs. 75%) [58].

Ongoing Pediatric Research for Telavancin

Telavancin is being studied in the pediatric population. There is 1 planned study examining the single-dose PK of the drug given at 10 mg/kg in pediatric subjects aged 1–17 years [202].

Ceftaroline

Ceftaroline is a recently approved broad-spectrum cephalosporin indicated for the treatment of MRSA infection [59]. Ceftaroline has bactericidal activity against gram-positive organisms as the drug binds penicillin-binding protein, preventing synthesis of the bacterial cell wall [59]. MRSA strains developed antibiotic resistance through the acquisition of PBP-2a, to which many cephalosporins and beta-lactams have low affinity. However, ceftaroline has been found to have a high affinity to PBP-2a and is effective in the treatment of MRSA infection [59]. The drug is highly effective against gram-positive bacteria and has been found in vitro to have MIC_{90} values of 0.5–2 μg/mL, 0.01–0.5 μg/mL, and 8 μg/mL against MRSA, streptococci, and vancomycin-resistant enterococci, respectively [60,61].

Pharmacokinetics of Ceftaroline

Ceftaroline is given as an IV infusion at a dosage of 600 mg every 12 hours in adults [105]. The PK of ceftaroline following single and multiple dosing has been studied in the adult population. Ceftaroline follows linear PK within a dosing range of 50–1000 mg [105]. The steady state V_d of ceftaroline following a single 600 mg dose of the drug was 20 L (range 18– 21), and the drug is 20% bound to plasma proteins [105]. The $T_{1/2}$ of the drug is approximately 2.5 hours [62,105]. The CL of the drug in adults is 8.7–9.6 L/h [62,105].

Ceftaroline and its metabolites are primarily excreted renally, with approximately 88% of the drug being recovered in the urine following a single 600 mg IV dose of radiolabeled drug [105]. The PK of ceftaroline has not been reported in children or infants.

Safety and Efficacy of Ceftaroline

The safety and efficacy of ceftaroline have been evaluated in a number of large clinical studies in adults. A study in adults (n=100) compared ceftaroline versus standard therapy for the treatment of complicated skin and skin structure infection [63]. Subjects were given either ceftaroline 600 mg every 12 hours or vancomycin 1 g every 12 hours. Only subjects given standard treatment could be switched from vancomycin to a penicillinase-resistant penicillin if baseline cultures indicated that the pathogen was susceptible. Adverse events occurred at similar rates in the ceftaroline-treated group and the standard therapy group (61% vs. 56%). The only adverse event to occur more commonly among ceftaroline-treated subjects was nausea (6% vs. 0%) [63]. Three serious adverse events occurred in ceftaroline-treated subjects, none of which were treatment-related [63]. Subjects given ceftaroline experienced fewer generalized infusion reactions than standard therapy (0% vs. 9%) [63]. Clinical cure rates at end of treatment were similar between ceftaroline and standard therapy (98% vs. 96%, respectively) [63].

Two large studies, CANVAS 1 (n=702) and CANVAS 2 (n=694), evaluated ceftaroline versus vancomycin plus aztreonam for the treatment of complicated skin and skin structure infection [64–66]. Subjects were either given ceftaroline at 600 mg every 12 hours or vancomycin at 1 g every 12 hours plus aztreonam 1 g every 12 hours. Integrated analysis of both trials showed that adverse events occurred at similar rates in both the ceftaroline- and vancomycin-treated groups. Drug-related adverse events in >3% of subjects that occurred more often in ceftaroline-treated subjects included nausea (6% vs. 5%) and diarrhea (5% vs. 4%). Pruritus occurred more often in subjects treated with vancomycin than in those treated with ceftaroline (8% vs. 4%) [66]. More subjects discontinued vancomycin plus aztreonam treatment than did those treated with ceftaroline (5% vs. 3%) [66]. Clinical efficacy as measured by cure rate in microbiologically evaluable subjects showed that ceftaroline was non-inferior to standard treatment (93% vs. 94%). However, clinical cure rates for ceftaroline-treated subjects were lower than standard therapy when the pathogen isolated was a gram-negative organism (85% vs. 100%) [66].

FOCUS 1 (n=613) and FOCUS 2 (n=627) were 2 large clinical trials that compared ceftaroline versus standard therapy with ceftriaxone for the treatment of community-acquired pneumonia [67,68]. Subjects were either given IV ceftaroline at 600 mg every 12 hours or IV ceftriaxone at 1g every 24 hours.

In the FOCUS 1 study, adverse events occurred at similar rates in ceftaroline-treated subjects and ceftriaxone-treated subjects (40% vs. 44%, respectively). No adverse event occurred in >5% of treated subjects. Common adverse events that occurred at >3% rate and more often in ceftaroline-treated subjects included diarrhea (5% vs. 2%), insomnia (3% vs. 2%), and headache (3% vs. 1%). Drug-related severe adverse events occurred less frequently in ceftaroline-treated subjects (2 subjects vs. 8 subjects). The 2 severe adverse events in ceftaroline-treated subjects included 1 case of sudden death and 1 abnormal liver function

test. At end of therapy, ceftaroline was found to have a higher cure rate for community-acquired pneumonia than ceftriaxone (88% vs. 80%) [67].

In the FOCUS 2 study, adverse events occurred at similar rates in ceftaroline-treated subjects and ceftriaxone-treated subjects (20% vs. 17%)—rates that were lower than those seen in FOCUS 1. Common adverse events that occurred at >3% rate and more often in ceftaroline-treated subjects included diarrhea (4% vs. 3%), headache (4% vs. 2%), and hypokalemia (3% vs. 2%). One drug-related severe adverse event, convulsion, occurred among ceftaroline-treated subjects. At end of therapy, ceftaroline showed non-inferiority to ceftriaxone for the treatment of community-acquired pneumonia (86% vs. 80%) [68].

Ongoing Pediatric Research for Ceftaroline

Ceftaroline is being studied in the pediatric population. One phase 1 study examining the PK of the drug in subjects aged 12–17 years has been conducted, the results of which have not been published. Also, 2 studies are recruiting patients: 1) a phase 3 comparator study of ceftaroline versus vancomycin for the treatment of skin and skin structure infection in pediatric patients; and 2) a phase 3 comparator study of ceftaroline versus ceftriaxone for the treatment of pediatric patients with community-acquired bacterial pneumonia [202].

Tigecycline

Tigecycline is a broad-spectrum glycylcycline antibiotic indicated for the treatment of MRSA infection [69,106]. The drug reversibly binds to the 30S ribosomal subunit, inhibiting the synthesis of bacterial proteins [69]. Tigecycline is generally thought to be bacteriostatic, but the drug does have bactericidal activity against gram-positive organisms at concentrations 4 times greater than the MIC_{90} concentration [70,106]. Tigecycline has been found in vitro to have MIC_{90} values of 0.25–1 μg/mL, 0.25 μg/mL, and 0.25 μg/mL against MRSA, streptococci, and enterococci, respectively [71,106].

Pharmacokinetics of Tigecycline

In adults, tigecycline is given as an IV infusion [106]. In adults, a 100 mg loading dose is initially administered, followed by a maintenance dose of 50 mg every 12 hours. The PK of tigecycline in adults has been studied following single and multiple dosing. Tigecycline follows linear PK for single doses of 12.5 mg to 300 mg and for multiple doses of 25–100 mg every 12 hours [72]. The steady state V_d of tigecycline following 50–100 mg dosing every 12 hours is 7.2–9.1 L/kg. Tigecycline is 73–91% bound to serum proteins at serum concentrations from 0.1–1 μg/mL [72,106]. The $T_{1/2}$ of the drug following a single 100 mg infusion has been found to be between 16.5 and 27.1 hours [73,106]. The CL of tigecycline is 0.2–0.3 L/kg/h (Table 2) [72]. The primary route of excretion of tigecycline and its metabolites is through biliary excretion (59%) and renal excretion (33%) [106].

The PK of tigecycline in children has been studied in 2 separate studies. Both studies aimed to determine tigecycline dosing such that the AUC measurements in children approximated $AUC_{0\text{-}24}$ levels in adults, as prior studies had shown the $AUC_{0\text{-}24}$/MIC ratio to be a good predictor of clinical response [74]. The first study examined the PK of tigecycline following an ascending dose in children aged 8–16 years. Based on the $AUC_{0\text{-}24}$ parameter, the study

authors concluded that a dose of 1 mg/kg every 12 hours in children above age 12 years most closely approximated adult AUC_{0-24} levels known to be therapeutically effective [75,106]. A subsequent phase 2 study (n=58) examined the PK of tigecycline in children aged 8–11 years [75]. Tigecycline was given to subjects enrolled in 3 different cohorts at dosages of 0.75 mg/kg every 12 hours, 1 mg/kg every 12 hours, or 1.25 mg/kg every 12 hours (Table 2). The estimated AUC_{0-24} values that most closely approximated adult values were observed in children receiving approximately 1.2 mg/kg tigecycline every 12 hours [75].

Safety and Efficacy of Tigecycline

The safety and efficacy of tigecycline have been evaluated in a number of large clinical studies in adults. One phase 3 study in adults (n=157) compared tigecycline versus standard therapy for the treatment of complicated skin and skin structure infection [76]. Subjects were given either tigecycline 100 mg loading dose followed by 50 mg every 12 hours or vancomycin 1 g every 12 hours. Adverse events occurred at similar rates in tigecycline-treated subjects and vancomycin-treated subjects (69% vs. 67%, respectively). Gastrointestinal adverse events occurred more frequently in tigecycline-treated subjects than in vancomycin-treated subjects, which included nausea (29% vs. 8%) and vomiting (19% vs. 3%). Serious adverse events occurred at similar rates in tigecycline- and vancomycin-treated subjects (20% vs. 21%, respectively), as did treatment discontinuation (7% vs. 5%, respectively) [76].

A second phase 3 study in adults (n=1116) also compared tigecycline versus vancomycin for the treatment of complicated skin and skin structure infection [77]. Subjects were given either tigecycline 100 mg loading dose followed by 50 mg every 12 hours or vancomycin 1 g every 12 hours. Treatment-emergent adverse events occurred more frequently in tigecycline-treated subjects than in vancomycin-treated subjects (68% vs. 61%, P=0.02) but were either mild in nature or deemed by investigators to not be due to study medication [77]. Gastrointestinal adverse events occurred more frequently in tigecycline-treated subjects than in vancomycin-treated subjects, which included nausea (35% vs. 8%) and vomiting (20% vs. 4%). Treatment discontinuation occurred at similar rates in tigecycline- and vancomycin-treated subjects (4% vs. 5%, P=0.2) [77].

There are few studies examining the safety and efficacy of tigecycline in the pediatric population. In 2010, the FDA warned that treatment with tigecycline was associated with an increased risk of death despite the drug having demonstrated non-inferiority to comparator medication for the treatment of skin and skin structure infection, community-acquired pneumonia, and intra-abdominal infection [78,106]. Pooled analysis of 13 randomized controlled trials found that tigecycline was associated with a 0.7% absolute increase in mortality or a 30% relative increase in mortality versus comparator drugs. Furthermore, pooled analysis showed that tigecycline was found to have a higher absolute non-cure rate of 2.9% versus comparator medication [78]. Possible reasons for this finding of increased mortality and lower absolute cure rate for tigecycline treatment versus comparator treatment include inadequate antimicrobial activity of the drug, inadequate dosing, and possible drug

toxicity [78]. Due to the finding of increased mortality in adults, further trials evaluating the safety and efficacy of tigecycline in the pediatric population have not been conducted [106].

Prior to the FDA warning, safety and efficacy data for the pediatric population was reported in one phase 2 study of tigecycline (n=58) previously described [79]. Children 8–11 years of age were given tigecycline at 0.75–1.25 mg/kg every 12 hours. Adverse events were reported by 79% of subjects: 50% of subjects experienced nausea. Five percent of subjects experienced serious adverse events including postoperative wound infection (2%), anal fistula (2%), and abdominal pain (2%). All serious adverse events resolved by the end of the study. Treatment discontinuation occurred in 4% of subjects [79].

Future Pediatric Research for Tigecycline

Tigecycline has had 1 completed phase 1 study that examined the PK of the drug in pediatric subjects aged 8–11 years. There are currently no other active or open trials for this drug in the pediatric population [202].

Expert Commentary

Antibiotic resistance continues to be a major healthcare concern. In the United States, from 1999 to 2008, the proportion of staphylococcal infections resistant to methicillin and the incidence of MRSA infection have increased substantially. Over the last 15 years, 6 drugs have been approved for the treatment of *S. aureus* infections. PK and safety data in infants are only available for linezolid and daptomycin.

To combat the increase in infections caused by antibiotic-resistant organisms, more drug research in infants is needed for recently approved medications. While it is encouraging that clinical trials in children are underway for non-labeled drugs such as ceftaroline, daptomycin, and telavancin, it should be noted that none of these clinical trials is enrolling infants.

Infants, especially premature infants, have a unique and developing physiology. Rigorous studies are needed to evaluate PK/pharmacodynamic (PD) properties in this population. Linear extrapolation of adult dosing to infants is not advisable as drug elimination pathways are not linearly related to body weight. There are many unique challenges to studying drugs in infants, leading to a paucity of pharmacology trials in this population. These challenges include low parental consent rates and limited blood volumes for PK analysis [80].

Opportunistic studies address some of these challenges. Many off-label drugs are already given to infants as part of standard medical care. As the drug is already being administered to the infant, parental consent is needed only for specimen collection. Investigators can avoid additional blood draws by conducting scavenged sampling of residual specimen from the lab following the completion of ordered tests, or sparse sampling of only 2–3 low-volume specimens that can be collected with routine laboratory draws. The development of micro-analytical techniques has increased the accuracy of PK data obtained from sparse sampling and scavenged sampling. Low-volume plasma drug assays and dried blood spot

sampling allow for the accurate measurement of drug concentrations from <100 μL and <30 μL of specimen, respectively.

Sparse and scavenged sampling data can be modeled using population PK/PD analyses to generate population estimates and account for sources of between-subject variability. Population estimates can then be used to obtain individual estimates for each subject. Opportunistic studies using sparse and scavenged sampling have already been conducted to describe the population PK of several drugs in premature infants including fluconazole, cefepime, and amoxicillin [81–83].

Current legislation in the form of the Best Pharmaceuticals for Children Act (BPCA) aims to increase clinical research in the pediatric population. The BPCA allows the FDA to issue specific written requests to drug sponsors requesting clinical trials in the pediatric population be performed, with the incentive of granting an additional 6 months of patent exclusivity to the drug sponsor should the trials be conducted. Moreover, under the Food and Drug Administration Innovation and Safety Act (FDASIA), the FDA must provide a specific rationale if written requests for future studies do not include neonates.

In the event that the drug sponsors choose to not fulfill the written request, the BPCA further gives the National Institutes of Health (NIH) the responsibility of creating a priority list of drugs needing further study in the pediatric population. The National Institute of Child Health and Human Development (NICHD) is responsible for the research of prioritized drugs, with the goal of improving pediatric therapeutics through clinical trials that lead to drug label changes.

Vancomycin is frequently the drug of choice for the treatment of serious MRSA infection in infants. Linezolid is approved by the FDA for use in premature and term infants. Linezolid has been studied in infants, and a dose of 10 mg/kg every 24 hours approximates adult dosing of 600 mg/day. The safety of linezolid in infants has been shown to be similar or better than vancomycin. Infants administered linezolid should have complete blood counts measured weekly due to associated myelosuppression. Although daptomycin is not FDA-approved for use in infants, the PK of daptomycin has been studied in infants, suggesting that the weight-normalized clearance of the drug in infants is higher than in adults. Due to the increased body weight-normalized CL of the drug in infants, doses of 6 mg/kg every 12 hours have shown a similar drug exposure to adult doses of 4 mg/kg every 24 hours. Although limited, data suggest daptomycin is well tolerated. Infants receiving daptomycin should have CK levels monitored.

Quinupristin/dalfopristin has been studied in non-infant pediatric populations. There are no PK, safety, or efficacy studies of the drug in infants. There are also no clinical trials actively enrolling patients to study quinupristin/dalfopristin use. Lastly, as quinupristin/dalfopristin is not indicated for the treatment of MRSA infection, we believe that there are better drug choices for the treatment of MRSA infection in infants. Ceftaroline and telavancin have been shown to be effective drugs for the treatment of MRSA infection in adults. However, neither drug has been studied in infants.

Five-Year View

Future treatment of MRSA infection in infants will come from drugs that are currently in phase 3 clinical trials. Newly developed antibiotics against gram-positive bacteria for the treatment of skin and skin structure infection include tedizolid, dalbavancin, oritavancin, and omadacycline [203]. One phase 1 PK study in adolescents has been completed for both tedizolid and dalbavancin [202]. There are currently no other active, open, or completed studies for either drug according to publicly available databases. No clinical trials in the pediatric population have been completed or are underway for oritavancin or omadacycline. Moreover, no infant studies for these 4 drugs are underway or have been completed according to ClinicalTrials.gov.

The 2003 Pediatric Research and Equity Act (PREA) mandated that a pediatric study plan be created for all new drug applications should the drug have a new active ingredient, indication, dosage form, dosing regimen, or route of administration [107]. The pediatric study plan should be created by the end of phase 2 of development and should include plans to study drug dosing, safety, and effectiveness in children. Extrapolation from adult data may be used to determine pediatric drug effectiveness. PREA mandates pediatric studies for all antibiotics that are in development, including tedizolid, dalbavancin, oritavancin, and omadacycline.

Investigators in collaborative research networks (e.g., Pediatric Trials Network, www.pediatrictrials.org) can continue to incorporate opportunistic studies into clinical research, as these studies are low-risk and have a high-yield potential.

Acknowledgments

Financial Disclosures

D.G. is funded by training grant T32GM086330 from the National Institute of General Medical Sciences. P.B.S. receives salary support for research from the National Institutes of Health (NIH), the U.S. Department of Health and Human Services, and the National Center for Advancing Translational Sciences of the NIH (HHSN267200700051C, HHSN275201000003I, and UL1TR001117); he also receives research support from industry for neonatal and pediatric drug development (www.dcri.duke.edu/research/coi.jsp). M.C.W. receives support for research from the National Institutes of Health (NIH) (1K23HD064814), the National Center for Advancing Translational Sciences of the NIH (UL1TR001117), the Food and Drug Administration (1U01FD004858-01), the Biomedical Advanced Research and Development Authority (BARDA) (HHSO100201300009C), the nonprofit organization Thrasher Research Fund (www.thrasherresearch.org), and from industry for drug development in adults and children (www.dcri.duke.edu/research/coi.jsp)

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Key Issues

- The proportion of staphylococcal isolates that are MRSA has increased, and the incidence of MRSA infection has increased 10-fold.
- Antibacterial agents that have been approved in adults over the past 15 years for the treatment of skin and skin structure infection caused by staphylococcal bacteria include linezolid, daptomycin, quinupristin/dalfopristin, ceftaroline, telavancin, and tigecycline.
- Of the 6 recently approved antibiotics, linezolid is the only antibiotic to be labeled for use in infants and premature infants.
- Clinical studies for ceftaroline, telavancin, and daptomycin are underway for pediatric patients. However, none of these studies is examining the drug in the infant population.
- Extrapolation of efficacy data from well-controlled adult trials is a possible method to accelerate drug labeling in infants and other pediatric populations.
- Antibiotics in phase 3 of development include tedizolid, dalbavancin, oritavancin and omadacycline. Few clinical trials have been completed for these medications in the pediatric population. No trials in infants are underway or have been completed for any of these drugs.

Expert Rev Clin Pharmacol. Author manuscript; available in PMC 2015 May 01.

Table 1

Drug indications, approval year, and approved population(s)

Drug	Year approved	Approved populations	Indications for *S. aureus* infections
Quinupristin/dalfopristin	1999	12 years and older	1) skin and skin structure infections (MSSA only)
Linezolid	2000	Birth to adult	1) pneumonia (MSSA and MRSA)
			2) skin and skin structure infections (MSSA and MRSA)
Daptomycin	2003	18 years and older	1) skin and skin structure infections (MSSA and MRSA)
			2) bacteremia (MSSA and MRSA)
Telavancin	2009	18 years and older	1) skin and skin structure infections (MSSA and MRSA)
			2) pneumonia (MSSA and MRSA)
Ceftaroline	2010	18 years and older	1) skin and skin structure infections (MSSA and MRSA)
			2) pneumonia (MSSA only)
Tigecycline	2005	18 years and older	1) skin and skin structure infections (MSSA and MRSA)
			2) intra-abdominal infections (MSSA and MRSA)

MRSA = methicillin-resistant *S. aureus*, MSSA = methicillin-susceptible *S. aureus*.

Table 2

Pharmacokinetic parameters following IV dosing

Drug	Population	Dose	C_{max} (mg/L)	AUC (mg/L*h)	$T_{1/2}$ (h)	CL (L/kg/h)
Linezolid	<1 week, preterm (n=9) [15,101]	10 mg/kg	13	108	5.6	0.12
	<1 week, term (n=10) [15,101]	10 mg/kg	12	55	3.0	0.23
	1–4 week, term (n=10) [15,101]	10 mg/kg	13	34	1.5	0.31
	1–3 months (n=12) [15,101]	10 mg/kg	11	33	1.8	0.32
	0.25–11 years (n=59) [15,101]	10 mg/kg	15	58	2.9	0.23
	12–17 years (n=36) [15,101]	10 mg/kg	17	95	4.1	0.13
	Adults (n=29) [15,101]	600 mg (~8.5 mg/kg)	13	91	4.9	0.10
Daptomycin	GA 23 week, PNA 70 days [29]	6 mg/kg every 12 hours	42	-	-	-
	GA 29 week, PNA 56 days [33]	6 mg/kg every 12 hours	13	-	-	-
	GA 32 week, PNA 25 days [29]	6 mg/kg every 12 hours	37	-	-	-
	GA 32 week (23,40) (n=20) [28]	6 mg/kg	26	262	6.2	0.02
	GA 34 week + 89 days [33]	6 mg/kg every 12 hours	11	-	-	-
	GA 38 week + 26 days [33]	6 mg/kg every 12 hours	18	-	-	-
	2–6 years (n=7) [27]	4 mg/kg every 24 hours	44	215	5	0.02
	7–11 years (n=8) [27]	4 mg/kg every 24 hours	48	271	6	0.02
	12–17 years (n=7) [27]	4 mg/kg every 24 hours	50	374	7	0.01
	Adult (n=6) [25,26]	4 mg/kg every 24 hours	58	414–494	8	0.01
	Adult (n=6) [24,25]	6 mg/kg every 24 hours	94–99	632–747	8–9	0.01
	Adult (n=6) [24,25]	8 mg/kg every 24 hours	123–133	858–1130	8–9	0.01
	Adult (n=9) [24]	10 mg/kg every 24 hours	141	1039	8	0.01
Quinupristin	Adult (n=10) [37]	7.5 mg/kg every 8 hours	2	2.6	0.8	0.90
	Adult (n=63) [37–40]	7.5 mg/kg every 12 hours	2–3	2.5–3.4	0.8–1.1	0.66–0.96
	Chronic renal failure (n=13) [38]	7.5 mg/kg every 12 hours	3	3.4	0.8	0.66
	Hepatic cirrhosis (n=16) [39]	7.5 mg/kg every 12 hours	4	3.5	0.9	0.72
Dalfopristin	Adult (n=10) [37]	7.5 mg/kg every 8 hours	6	6.4	0.5	0.90
	Adult (n=63) [37–40]	7.5 mg/kg every 12 hours	6–8	6.2-8.3	0.5–1.0	0.72–0.90

Drug	Population	Dose	C_{max} (mg/L)	AUC (mg/L*h)	$T_{1/2}$ (h)	CL (L/kg/h)
	Chronic renal failure (n=13) [38]	7.5 mg/kg every 12 hours	9	10.1	0.6	0.60
	Hepatic cirrhosis (n=16) [39]	7.5 mg/kg every 12 hours	7	7.4	0.7	0.66
Telavancin	Adult (n=7) [51]	7.5 mg/kg every 24 hours	90	668	8	0.01
	Adult (n=7) [51]	15 mg/kg every 24 hours	181	1239	7	0.01
	Adult (n=39) [53]	7.5 mg/kg every 24 hours	88	599	6	0.01
	Adult (n=34) [53]	15 mg/kg every 24 hours	186	1282	8	0.01
Ceftaroline	Adult (n=11) [61]	600 mg every 12 hours	28	62	2.5	8.7 L/h
	Adult (n=6) [105]	600 mg every 12 hours	21	57	2.6	9.6 L/h
Tigecycline	8–11 years (n=17) [74]	0.75 mg/kg every 12 hours	0.6	1.7	-	0.49
	8–11 years (n=21) [74]	1 mg/kg every 12 hours	1.5	2.6	-	0.50
	8–11 years (n=20) [74]	1.25 mg/kg every 12 hours	2.6	3.2	-	0.53
	Adult (n=6) [71]	25 mg every 12 hours	0.3	1.5	50	0.20
	Adult (n=6) [71]	50 mg every 12 hours	0.6	3.1	37	0.20
	Adult (n=6) [71]	100 mg every 12 hours	1.1	5.0	67	0.24

C_{max} = maximum concentration of drug, AUC = area under the concentration curve, $T_{1/2}$ = half-life of the drug, CL = systemic clearance rate of the drug, GA = gestational age, PNA = postnatal age. “–” denotes information is not available. Mean or median reported. Adult data are from non-obese individuals.