



## Treatment option for sepsis in children in the era of antibiotic resistance

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EXPERT  
REVIEWSTreatment option for sepsis  
in children in the era of  
antibiotic resistance*Expert Rev. Anti Infect. Ther.* 12(10), 1237–1252 (2014)Irja Lutsar\*<sup>1</sup>,  
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Sepsis caused by multidrug-resistant microorganisms is one of the most serious infectious diseases of childhood and poses significant challenges for pediatricians involved in management of critically ill children. This review discusses the use of pharmacokinetic/dynamic principles (i.e., prolonged infusion of  $\beta$ -lactams and vancomycin, once-daily administration of aminoglycosides and rationale of therapeutic drug monitoring) when prescribing antibiotics to critically ill patients. The potential of 'old' agents (i.e., colistin, fosfomycin) and newly approved antibiotics is critically reviewed. The pros and cons of combination antibacterial therapy are discussed and finally suggestions for the treatment of sepsis caused by multidrug-resistant organisms are provided.

**KEYWORDS:** antibiotic • MDR gram-negatives • MDR gram-positives • PK/PD • TDM

Severe sepsis in children is a major healthcare problem with about 75,000 cases occurring in 2005 in the USA [1]. The incidence is highest in infants (5.16 per 1000) and lowest in older children accordingly [2]. About half of the septic children have serious underlying conditions of which prematurity in the first year of life and immunologic/hematologic and neoplastic disease in older age groups are the most common. With the hospital mortality rate of 10% in general and about 23% of cases caused by multidrug-resistant gram-negative (MDR-GN) organisms, sepsis is by far the most serious infectious disease in childhood [2,3]. The most common infecting organism of sepsis in the USA was *Staphylococcus* (17.5% overall), especially among neonates [2]. Opportunistic microorganisms that are common colonizers of GI tract are mainly associated with nosocomial infections, but the border between community- and hospital-acquired infections in the era of modern medicine is blurred.

Antibiotic resistance, especially emergence of MDR-GN organisms is in rise and poses clinical problems in adults as well as in children with sepsis. MDR pathogens (with resistance to at least three different classes of antibiotics) are reported with increasing frequency and pan-resistant strains (not susceptible to any registered antibiotics) have already appeared [4,5]. This

phenomenon is threatening, since treatment options for infected patients are extremely limited [6–8]. The situation in low- and middle-income countries is even worse than in the developed world. About 70% of hospital-acquired neonatal infections in developing countries could not be successfully treated by the regimen recommended by WHO [9]. A study in Tanzanian children confirmed that ineffective treatment of bloodstream infections due to antibiotic-resistant bacteria predicted fatal outcome independent of underlying diseases [10]. The key factors driving antibiotic resistance are over- and misuse of antibiotics selecting MDR strains, globalization promoting the spread of successful clones and suboptimal hospital hygiene enabling spread of resistant clones.

At the same time, the pipeline of new antimicrobial agents with activity against resistant organisms is dry. A search of three commercial databases on the antibiotic research and development pipeline identified 66 new active substances with antibacterial properties. Fifteen of these were assessed as acting via a new or possibly new mechanism or on a new or possibly new target. Out of these, 12 agents had documented *in vitro* activity against antibiotic-resistant gram-positive bacteria and only 4 against antibiotic-resistant gram-negative bacteria [11]. The lack of new antibiotics is further

complicated by the fact that even if they become available for adults, pediatric dosing recommendations and safety data are often missing or are limited to small studies or case reports, making the use of these agents in pediatrics uncertain [12].

### Microorganisms commonly associated with antibiotic resistance

The epidemiological studies exclusively conducted in children are rare or small; often susceptibility of pediatric isolates is reported together with adult isolates. As antibiotic-resistant organisms in children may originate from community or hospital, one could speculate that antibiotic resistance pattern in both populations is similar. Antibiotic Resistance and Prescribing in European Children (ARPEC) project, a pan-European project, was exclusively conducted in children and included 10 European countries and 18 hospitals in 2011–2012. Similar to the European Antimicrobial Resistance Surveillance Network, antibiotic susceptibility was reported for key microorganisms associated with invasive disease [13].

### Penicillin-resistant *Streptococcus pneumoniae*

*S. pneumoniae* is the most common cause of community-acquired pneumonia but cases of sepsis have been described as well [14]. The first outbreaks of infection due to penicillin-resistant *S. pneumoniae* (PRSP) occurred in 1977 and 1978 in South Africa [15,16]. Penicillin resistance in pneumococci is caused by mutations in the penicillin-binding proteins (PBP) needed for synthesis of peptidoglycan. Six PBPs have been identified in pneumococci (1A, 1B, 2A, 2B, 2X, 3). Mutations lead to reduction of penicillin-binding affinity, but it can be overcome by using higher doses of antibiotics.

In the ARPEC project, the PRSP rate varied from 12% in Southern Europe to 35% in Western Europe; resistance rates in northern European countries were low, that is, <10% [13].

The acquisition of a cassette of genetic elements that encode resistance to penicillin leads to resistance to other antibiotics (e.g., macrolides, quinolones, clindamycin) as well. Many PRSP strains have alterations in PBPs, especially PBP 2X and 1A, that also make them resistant to third-generation cephalosporins. PRSP strains harbor more likely co-resistance to macrolides, triggered by *erm(B)* (alteration of macrolide binding site in ribosome) and *mef* gene (antibiotic efflux pump system). In contrast to PBP mutations, the *ermB* gene expression leads to high-level resistance (MIC >128 mg/l) to macrolides, lincosamines and streptogramin B. The concentrations exceeding 128 mg/l can hardly be safely achieved by increasing the dose and these strains require treatment with different antibiotics. Dual  $\beta$ -lactam/macrolide resistance is becoming more prevalent, especially in serotypes commonly found in children (serotypes 6A, 6B, 14, 15A, 19A, 19F) [17].

### Methicillin-resistant *Staphylococcus aureus* & *Staphylococcus epidermidis*

*Staphylococcus aureus* is a common cause of skin and soft tissue infections, bacteremia, osteomyelitis, endocarditis and other

invasive infections in children. Coagulase-negative staphylococci (CoNS; mostly *Staphylococcus epidermidis*) are the predominant agents of late-onset sepsis in very-low-birth-weight infants [18,19]. In children with hematological malignancies, CoNS have equal frequency with *Enterobacteriaceae* (median 23%) in causing bloodstream infections as demonstrated in the review of 16 studies from various countries [20]. About 90% *S. epidermidis* strains are methicillin-resistant and thus with a few exceptions not susceptible to  $\beta$ -lactams. Methicillin resistance, first described in 1961, is conferred by the *mecA* gene, which encodes PBP2a with decreased affinity to  $\beta$ -lactam antibiotics. Until the late 1990s, a few clones circulating in healthcare settings accounted for most methicillin-resistant *S. aureus* (MRSA) infections. In the 21st century, two main clones circulate: USA 100 is the predominant hospital-acquired MRSA and USA 300 is the predominant community-acquired MRSA [21].

The prevalence of MRSA in Europe varied from 1.3% in Denmark to 54% in Portugal and Romania in 2012 [22]. According to the ARPEC data, MRSA accounted for 15% of all invasive *S. aureus* isolates; again the incidence was highest in southern (24%) and lowest in northern parts of Europe (4%) [13]. In the USA, nearly 60,000 children with *S. aureus* infection were hospitalized from 2002 to 2007; MRSA accounted for 51% of cases [23]. More recently, the rate of MRSA has stabilized in many European countries [24,25].

In 2002, vancomycin-resistant strain of *S. aureus* with MIC >32  $\mu$ g/ml was reported. This time resistance was triggered by gene cluster *vanA* acquired most probably from vancomycin-resistant enterococci (VRE) [26]. Few cases of vancomycin-resistant strain of *S. aureus* have been reported worldwide [27,28]. The impact of vancomycin-resistant strain of *S. aureus* for pediatric population is not known.

### Vancomycin-resistant enterococci

Serious enterococcal infections are rising in neonatal, intensive care and oncology units [29]. High-level resistance to vancomycin is encoded by different clusters of genes referred to as the vancomycin resistance gene clusters (e.g., *vanA*, *vanB* and *vanD* gene clusters) resulting in the replacement of D-Ala-D-Ala ending of peptidoglycan precursors with D-alanyl-D-lactate termini, to which vancomycin binds with significantly lower affinity. The replacement of D-alanine by D-lactate increases the MIC of vancomycin almost 1000-fold [30].

*VanA* enterococci are resistant to high levels of vancomycin (MIC  $\geq$ 64  $\mu$ g/ml) and teicoplanin (MIC  $\geq$ 8  $\mu$ g/ml). *VanB* organisms are resistant to a range of vancomycin concentrations, from 4 to >1024  $\mu$ g/ml [31]. High-level resistance is usually associated with *Enterococcus faecium*.

At present, reported VRE prevalence rates vary from 0 in Eastern and Northern Europe to 44% in Ireland [22].

### Multidrug-resistant gram-negative organisms

MDR-GN organisms have emerged and are characterized by high mortality rates. They include *Enterobacteriaceae* producing extended-spectrum  $\beta$ -lactamases (ESBL) and carbapenemases;

MDR *Pseudomonas aeruginosa* and *Acinetobacter baumannii*.  $\beta$ -Lactamases are enzymes that inactivate  $\beta$ -lactam antibiotics by hydrolyzing the  $\beta$ -lactam ring. ESBLs are able to inactivate most  $\beta$ -lactam antibiotics, including most penicillins, cephalosporins and the monobactam aztreonam [31,32]. There are three major groups of ESBLs: TEM, SHV and CTX-M. The genes determining ESBL production are located in plasmids and therefore have a good potential to spread [33].

MDR-GN bacteria account predominantly for nosocomial infections such as ventilator-associated pneumonia, complicated urinary tract, intra-abdominal but also bloodstream infections and neonatal sepsis [34,35].

Despite the rising relevance of MDR-GN infections in adults, only a few studies have evaluated this problem in pediatric population. Those that have, observed large geographical variations, the rates ranged from 4 to 6% in North America and Europe to 17% in Asia Pacific and Latin America [36]. Slightly higher numbers were observed in the ARPEC study: 13% of invasive isolates of *Escherichia coli* and 32% of *Klebsiella pneumoniae* were resistant to higher class cephalosporins suggestive of ESBL production [13].

More recently, carbapenem-resistant (CR) *Enterobacteriaceae* due to the production of carbapenemases or alterations/loss of porins have emerged. At present, the prevalence of CR *K. pneumoniae* in general varies between 4 and 6% [37], but rates up to 60% have been reported in some countries (e.g., Greece) [22]. In the ARPEC study, the CR resistance was low, that is, <1% in *E. coli* and 6% in *K. pneumoniae* [13].

Non-fermentative microorganisms *P. aeruginosa* and *A. baumannii* have a wide capacity to resist antibiotics, either intrinsically (due to  $\beta$ -lactamases, efflux pumps and low permeability of outer membrane, decreased expression of porins) or following acquisition of resistance genes (increased production of antibiotic-inactivating enzymes, antibiotic target modification) [34,38–40].

In otherwise healthy children and in those younger than 5 years, *P. aeruginosa* infection is extremely rare. Most reported cases involve patients with serious underlying conditions (e.g., hematological malignancies, cystic fibrosis [CF] and prolonged hospitalization to ICU). In ARPEC study, 32% of *P. aeruginosa* strains were CR, 30% resistant to high-generation cephalosporins, 27% to aminoglycosides (AG) and 24% to fluoroquinolones [13]. *A. baumannii* is almost always associated with nosocomial spread and outbreaks and rarely affects previously healthy children [41–43]. According to European Antimicrobial Resistance Surveillance Network, up to 51% of isolates of *A. baumannii* spreading in Europe in 2012 were MDR [22].

### General concept in management of infections caused by MDR microorganisms

The treatment of sepsis caused by MDR microorganisms is frequently limited to one of three strategies. The first option is to administer first-line antibiotics (i.e., meropenem, cefepime, vancomycin) at higher doses and/or as prolonged infusions to overcome resistance. However, if the microorganisms exhibit

very high MICs to first-line agents, extremely high doses with unacceptable toxicity would be needed to achieve exposures required for efficacy. The second choice is to use an old antibiotic (i.e., colistin, fosfomycin) or a new agent with good activity against MDR isolates. Unfortunately, second-line agents are more toxic than first-line agents and prone to rapid resistance development. Thus, monotherapy may not be feasible. In addition, the dosing regimens of new agents in children are mostly absent and clinical experience on their use is largely missing [12]. The final strategy for treating MDR infections is to combine first- and second-line antibiotics with the hope that synergistic interactions between antibiotics will lessen the need for extremely high doses, suppress the emergence of resistance and overcome the pharmacokinetic (PK) weaknesses of individual agents. The risk of cumulative toxicity may become an issue. All these options are discussed below.

### Improving PK/PD properties of first-line antibiotics

Site of infection, body size, disease severity and age affect volume of distribution ( $V_d$ ) and drug elimination [44,45]. In septic patients, changes in physiology like altered protein binding, poor tissue penetration (perfusion) and disease-related fluctuations in  $V_d$  and clearance (CL) lead to further variation in drug concentrations, compromising safety but also efficacy [46,47]. Disease severity and host immunologic status affect dose-response relationship with higher PK/pharmacodynamic (PD) indices required for success in the critically ill [46,48]. Higher PK/PD targets may also be needed for sites with poor tissue penetration, like lung or CNS [49–51]. Subtherapeutic antibiotic levels may promote the selection of resistant pathogens [45]. Additional role of bacterial load in eradication (effective PK/PD target) as well as resistance emergence has been suggested by *in vitro* studies with much higher PD targets compared with clinical efficacy needed to prevent resistance [52,53].

### Aminoglycosides

AG are concentration-dependent antibiotics in which maximum serum concentration ( $C_{max}$ ) over MIC ( $C_{max}/MIC$ ) or area under the time concentration curve over MIC (AUC/MIC) of the infecting pathogen is the main efficacy related PD parameter [54–56]. Optimum therapeutic response is achieved at AG  $C_{max}/MIC$  exceeding 8–10 or AUC/MIC 75–150 [55,57]. This concept has led to the recommendation of higher unit doses, resulting in earlier achievement of therapeutic concentration and higher  $C_{max}/MIC$ ; administered at longer intervals [55,58,59]. As reabsorption of AG in proximal renal tubules is saturable, favorable nephrotoxicity profile could also be expected. Both, animal and human data have found more fractionated administration to result in higher drug concentrations in tubular epithelial cells [60,61]. The concern that longer drug-free period during prolonged dosing intervals potentially exceeds the post-antibiotic effect of AG and allows regrowth of bacteria, is not well supported by evidence, although some uncertainty in relation to resistance development exists. Once (ODD) but not multiple daily (MDD) high-dose tobramycin

has been reported to result in increased MIC of *P. aeruginosa* in CF [58].

When targeting pathogens with higher MIC values (>1 mg/l), ODD administration of the currently recommended daily doses of 4–7 mg/kg for gentamicin, 15–20 mg/kg for amikacin or 6–7.5 mg/kg for tobramycin has a greater potential to achieve  $C_{\max}/\text{MIC}$  ratio of 8–10. In neonates, a meta-analysis of 11 trials comparing gentamicin ODD versus MDD found the former to result in improved PK/PD profile with less failures to attain target gentamicin peak (>5 mg/l) and trough levels (<2 mg/l) [62]. All infants in both regimens showed adequate resolution of sepsis. Another meta-analysis of 24 randomized clinical trials (RCT) evaluating ODD versus MDD AG administration found overall comparable efficacy in pediatric population [63]. Significantly lower clinical or microbiological failure rate in ODD compared with MDD regimen was seen in trials using amikacin (10/114 vs 25/112; risk ratio; 95% CI: 0.41; 0.22–0.77).

Zakova *et al.* retrospectively evaluated the feasibility of gentamicin ODD regimen in 140 critical care children and found that with 6 mg/kg the highest percentage of patients achieved  $C_{\max}$  (16–20 mg/l), and drug-free interval within target ranges simultaneously [64]. In neonates, gentamicin 6 mg/kg with a dosing interval of 24 h in post-menstrual age (PMA)  $\geq 29$  weeks and 36 h in PMA <29 weeks was associated with trough concentrations exceeding 2 mg/l in only 6% of episodes [65]. In 86 children (61% with febrile neutropenia), treated for 106 episodes of suspected sepsis with gentamicin 7 mg/kg trough values were within the 24 h range of the Hartford nomogram in 100% of cases. Permanent hearing loss was seen in 2% and transient nephrotoxicity in 1%; in all cases additional risk factors were present [66]. In children with febrile neutropenia, tobramycin ODD regimen to achieve  $C_{\max}$  of 20–22.5 mg/l and a drug-free interval ( $C_{\text{drug}} < 1$  mg/l) of 4 h required initial doses of 10 mg/kg for patients aged 6 months to 9 years, 8 mg/kg for those aged 9–12 years and 6 mg/kg for children aged >12 years [67]. Amikacin doses of 25 mg/kg have been advocated in adults with sepsis [68]. As an extreme, successful monotherapy with 25–50 mg/kg/day of amikacin and concomitant renal replacement therapy to reduce adverse effects has been reported in an adult with MDR-GN sepsis [69].

### Toxicity

Higher doses inevitably result in higher risk of toxicity [55]. AG nephrotoxic potential increases from amikacin to tobramycin and netilmicin to gentamicin [70]. Pre-existing renal dysfunction, hypovolemia, shock, liver dysfunction as well as previous and concurrent exposure to other nephrotoxic drugs, all frequently present in sepsis, are risk factors for renal toxicity [50]. Adult studies show decrease in renal toxicity with prolonged dosing intervals [61]. In children, who have a significantly lower rate of AG-induced renal injury compared with adults, the meta-analysis found no difference in the rise in serum creatinine or decrease in creatinine CL between ODD versus MDD regimen [63]. A number of biochemical markers including

$\beta 2$ -microglobulin, urinary casts, urine AG (gentamicin), *N*-acetyl- $\beta$ -D-glucosaminidase and alanine aminopeptidase concentration and urinary metabolic profile have been studied, yet no successful strategy is currently implemented [50,71].

While AG-related nephrotoxicity is reversible in most cases, ototoxicity, manifesting as cochlear or vestibular toxicity, is irreversible. The total plasma AUC, proportional to the AUC in cochlear perilymph, has been suggested as the main determinant of ototoxicity. Hence, regimens that use the same total daily dose and duration result in similar ototoxicity rates. In the above-mentioned meta-analysis, the pooled ototoxicity rates for studies that provided auditory testing results were 2.3% (10 of 436 cases) in the ODD and 2.0% (8 of 406 cases) in the MDD arms with the fixed-effects risk ratio of 1.06 (95% CI: 0.51–2.19) [63]. Cumulative dose and duration appears the strongest predictor of ototoxicity [72,73]. A recent study of 23 children undergoing cancer therapy found amikacin cumulative dose of more than 1200 mg/kg and duration exceeding 50 days to be associated with 68–71% rate of hearing loss [74,75].

### The role of therapeutic drug monitoring

Prolonged dosing intervals together with short duration of treatment make therapeutic drug monitoring (TDM) in guiding AG therapy often impractical. A recent study of 79 children (aged 1 month to 16 years) treated with ODD gentamicin at 7 mg/kg/day concluded that TDM (using a nomogram) neither predicted nor prevented toxicity [66]. Monitoring of  $C_{\min}$  is advocated as cost-effective in populations at high risk of toxicity, like patients with organ failure, and for AG treatment lasting more than 5 days. Targets vary from 0.5 to 1 or 2 mg/l for gentamicin, tobramycin or netilmicin and 2.5–5 mg/l for amikacin [50]. A more targeted approach with a single  $C_{\min}$  measurement (after the first dose) and subsequent individual PK-based dose adjustment has been suggested [76]. However, one should bear in mind that after first dose steady state has not been achieved yet.  $C_{\max}$  monitoring is not routinely recommended as it results in additional economic burden with little or no added clinical value [77]. It may be advantageous to optimize efficacy when targeting pathogens with very high AG MIC [50].

### $\beta$ -Lactams

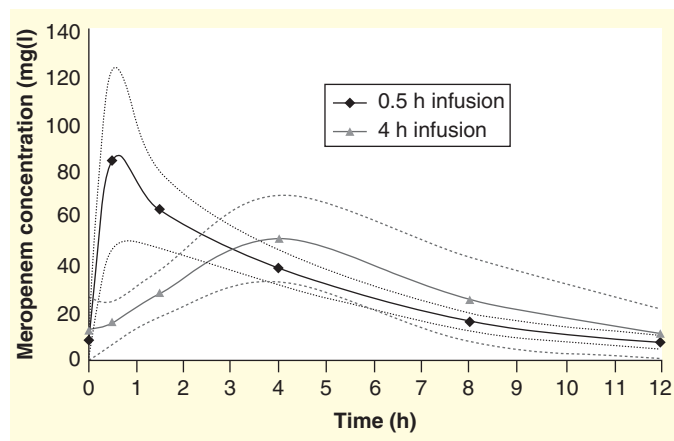
All  $\beta$ -lactam antibiotics are time-dependent and thus the time during which the free (unbound fraction) drug concentration remains above the MIC ( $fT > \text{MIC}$ ) is the dominant PK/PD index associated with bacterial killing [46,78] and clinical outcome [79–81]. The maximum killing by  $\beta$ -lactams occurs at concentrations, exceeding the MIC of a pathogen by approximately four- to five-times. Further increase in concentration does not provide additional benefit. Higher  $fT > \text{MIC}$  can be reached with higher doses (and increased dose fractionation) and/or prolonged/continuous infusion of  $\beta$ -lactams (FIGURE 1) [79,81,82].

With current intermittent  $\beta$ -lactam dosing regimens under-dosing appears frequent in adult ICU populations with

extremely wide variations in individual drug exposure [45]. A large multicenter ICU study found that 16% of 248 patients treated for infection did not achieve the 50% fT > MIC [81]. Positive clinical outcome was associated with 50% fT > MIC with further effect seen when increasing to 100% fT > MIC ratios (odds ratio [OR]: 1.02 and 1.56, respectively;  $p < 0.03$ ). Significant interaction with sickness severity status was observed. However, four meta-analyses of existing clinical studies comparing continuous infusion of  $\beta$ -lactams over intermittent bolus dosing have failed to prove higher cure rates or mortality benefit [83–86]. Retrospective and non-randomized studies, however, have reported improved outcomes with continuous or prolonged infusion of  $\beta$ -lactams [85,86]. In addition to methodological flaws (inadequate allocation sequence generation, allocation concealment, lack of intention-to-treat analysis, lower doses used in prolonged infusion arm), only a few RCTs have addressed populations at high risk of MDR infections [84,85]. A recent double-blind, RCT of continuous infusion versus intermittent bolus dosing of piperacillin-tazobactam, meropenem and ticarcillin-clavulanate in 60 patients treated in five intensive care units found higher clinical cure rate in the continuous group (70 vs 43%;  $p = 0.037$ ), but ICU-free days (19.5 vs 17 days) and survival (90 vs 80%) were similar [79]. Survival benefit with prolonged infusion compared to bolus dosing of cefepime in bacteremia or pulmonary infection due to *P. aeruginosa* has been suggested [87].

In pediatric patients, simulation studies have demonstrated improved therapeutic target attainment with prolonged (3 or 24 h) compared to 0.5 h infusion of cefepime, ceftazidime, imipenem/cilastatin, meropenem and piperacillin/tazobactam [82]. A meta-analysis including one RCT, five PK studies, two PD studies of Monte Carlo simulation, one case series and seven case reports also support the use of extended infusion in pediatric patients [88]. The only prospective clinical trial using continuous infusion of ceftazidime in CF, however, failed to demonstrate any clinical benefit over traditional dosing [89].

In a modeling study in adults, Rhodes *et al.* showed that prolonged or continuous infusion of  $\beta$ -lactams without a loading dose may delay time to effective antimicrobial plasma concentrations, especially for microorganisms with high MIC values (FIGURE 1) [80]. The latter in turn is a major predictor of survival in severe sepsis and septic shock [90]. Children, especially preterm neonates have higher body size adjusted Vd, further increased in severe infection [91]. The significantly higher body size adjusted doses of most  $\beta$ -lactams used in children compared with adults do not necessarily overcome this effect. Therefore, initial loading dose is needed when using prolonged infusions. Developmental changes in organ function, especially over the first few weeks of life, may require further dose adjustments. Bertels *et al.* found cefotaxime continuous infusion of 100 mg/kg/day (without loading dose) in neonates and children result in plasma concentrations ranging from 0.6 to 182.6 mg/l on day 1 [92]. Significant increase in cefotaxime CL over the first week of life and subsequent negative correlation between cefotaxime concentration and glomerular filtration rate



**Figure 1.** Time concentration curves of meropenem doses of 20 mg/kg administered as 0.5 h (black diamonds) versus 4 h (grey triangles) infusion in preterm neonates.

Dotted lines represent standard deviation.

Data are presented in [93].

was seen. In very preterm neonates with relatively long half-life and low CL of renally eliminated drugs, Padari *et al.* found little improvement of the fT > MIC with prolonging 20 mg/kg q12h meropenem infusion time from 30 min to 4 h in the treatment of infections caused by susceptible (MIC  $\leq 2$  mg/l) microorganisms [93]. Similar to an earlier study, benefit of prolonged infusion on modeled PK/PD parameters (T > MIC) was suggested with MIC increasing to 4–8 mg/l [94].

When applying prolonged administration, drug stability needs to be considered. Several  $\beta$ -lactams have good (piperacillin/tazobactam, ticarcillin/clavulanate and aztreonam) stability at body temperature, whereas others are stable for 24 h only at lower temperatures (cefepime, ceftazidime, doripenem and meropenem) [95,96]. In very small infants, substantial delay and variability in the rate of drug delivery due to low infusion rates of small fluid volumes can occur [97]. Terminal injection line incompatibility may further compromise efficacy.

In children no data on TDM of  $\beta$ -lactams are available. Studies in adults do not support its routine use in unselected populations. Scenarios, where TDM allows overcoming variations in PK include hypoalbuminemia, augmented renal CL, kidney injury with renal replacement therapy and possibly infection sites with poor drug penetration or targeting more virulent or less susceptible microorganisms [47].

### Vancomycin

The continuous infusion of vancomycin has been advocated with the aim of improving bactericidal efficacy and decreasing off-target concentrations and/or need for TDM [98,99]. The PK/PD index found to best correlate with clinical efficacy for vancomycin is the AUC/MIC ratio. Concerns about increasing MIC in staphylococci and improved efficacy associated with vancomycin AUC/MIC >400 in adults with MRSA pneumonia have led to recommendations to aim for trough vancomycin levels of 15–20 mg/l when treating pathogens with vancomycin

MIC >1 mg/l [100]. Intermittent bolus regimens targeting as high trough concentrations have not been proven safe. A recent meta-analysis incorporating five RCTs found lower risk of nephrotoxicity in adult patients receiving vancomycin as continuous infusion compared with bolus dosing, although it failed to show differences in efficacy [101].

Current data from neonatal studies including a variety of continuous infusion regimens with and without loading dose are inconclusive. Similar to  $\beta$ -lactams, the larger Vd and lower CL in neonates compared with adult population as well as aiming at fast achievement of therapeutic concentration mandate an initial loading dose to reach timely steady state concentration. Reported first concentrations (taken mostly 24–48 h after start of infusion) within the target range have been achieved in 71–89% of infants receiving vancomycin as continuous infusion [98,102–104]. Large inter-individual variability seen in all studies mandates the need for TDM. Even individual PK model based loading and subsequent continuous infusion dose calculation incorporating current weight as a determinant of Vd; current weight, post-natal age and serum creatinine as determinants of CL resulted in first TDM concentrations within the target range of 15–25 mg/l in only 71% of cases [104]. Target range was achieved in all cases after dose adjustment, suggesting lower need for subsequent TDM.

Unfortunately, none of these studies had adequate study design or power to draw definite conclusions on clinical efficacy in comparison to bolus dosing. In one study with continuous infusion, 92% treatment success within 4 days without removal of indwelling catheters was reported [102]. In children, anecdotal evidence supports improved efficacy of continuous vancomycin infusion in difficult-to-treat infections with increased vancomycin MIC. Fung described adequate serum levels of vancomycin followed by clinical success in three children with CF and MRSA infection, in whom target serum levels could not be achieved with conventional bolus dosing despite repeated dose adjustments [105].

### New antibiotics for resistant microorganisms

A total of 11 new antibacterial agents have been approved in the EU from 2000 to 2010; 5 of them potentially useful for the treatment of sepsis. Out of 11, only ertapenem and retapumilin have pediatric dosing recommendations but neither of them can be used for treatment of severe sepsis [12]. The newly approved agents that could be potentially used for the treatment of sepsis caused by resistant organisms are reviewed below.

Ceftaroline fosamil is a novel broad-spectrum parenteral cephalosporin with activity against several gram-positive microorganisms including MRSA and PRSP [106]. In adults, ceftaroline fosamil is recommended for treatment of complicated skin and soft tissue infections and community-acquired pneumonia at a dose of 600 mg b.i.d. The dosing regimens for children have not yet been established but several pediatric trials are ongoing [107].

Daptomycin is a cyclic lipopeptide with concentration-dependent activity against gram-positive microorganisms,

including MRSA and VRE. In adults, daptomycin is indicated for the treatment of complicated skin and soft tissue infections, staphylococcal bacteremia and right-sided endocarditis but not for pneumonia due to its interactions with pulmonary surfactant. The treatment experience with daptomycin is limited in children [12]. Two single-dose PK studies in children aged 2–17 years have been performed and showed the higher CL of daptomycin in younger children as compared to adolescents and adults. This suggests that higher doses (8–10 mg/kg) and twice-daily administration is needed in age between 2 and 12 years to achieve similar exposure to adults [108,109]. The PK data in neonates, however, are scarce but indicate the need of higher doses as well [110,111].

Doripenem monohydrate is the newest carbapenem indicated for treatment of complicated urinary tract infections, ventilator-associated pneumonia and complicated intra-abdominal infections in adults. *In vitro* doripenem is the most active carbapenem against *P. aeruginosa*, displaying higher percentage susceptibility than either imipenem or meropenem but overall, the susceptibilities of the MDR isolates are similarly low for all available carbapenems [112]. The clinical studies of doripenem in children are absent, but according to adult data, it is unlikely to be advantageous over the other carbapenems in the treatment of sepsis caused by MDR microorganisms.

Tigecycline is the first member of the glycylcyclines. It is a bacteriostatic antibiotic structurally related to tetracycline. Tigecycline covers a variety of gram-positive (including MRSA, VRE) but also difficult-to-treat gram-negative bacteria (*Stenotrophomonas maltophilia*, *A. baumannii* including ESBL and/or AmpC-producing and MDR *Enterobacteriaceae*, *K. pneumoniae* carbapenemase) [113,114]. Thus, it would be an excellent candidate for the treatment of infections caused by highly resistant microorganisms. A PK study in children aged 8–11 years revealed a dosage of ~1.2 mg/kg q12h to be the most appropriate. With this dose, up to 82% of patients achieved therapeutic target [115]. Tigecycline has similar side effects to the tetracycline, such as diarrhea, nausea and vomiting. However, in a meta-analysis of RCTs in nosocomial pneumonia and bloodstream infection, higher overall mortality rate in tigecycline-treated patients versus comparator drugs that achieve higher concentrations in the lung and bloodstream was observed [116]. Therefore, in children with sepsis similar to adults, the use of tigecycline should be restricted to situations where no alternatives are available. No studies have reported the use of tigecycline in children below 8 years of age.

Linezolid is the first member of the oxazolidinones with specific activity against gram-positive organisms including MRSA, methicillin-resistant *S. epidermidis*, VRE and PRSP. The US FDA-labeled linezolid for pediatric use in 2002 at doses of 10 mg/kg q8h in children aged 0–11 years and 10 mg/kg q12h (maximum 600 mg q12h) in older children. The experience of using linezolid has been gathered mainly from patients with serious underlying conditions (oncological patients, premature infants) who have failed treatment with other antibiotics; the response rate to linezolid therapy of around 75% has been

reported [117,118]. Altogether 25–29% of patients reported side effects (mainly hematological penias, increased liver function tests and skin rash). Adverse events were reversible in most cases and led to discontinuation of linezolid treatment in less than 5% of patients [117].

### Potential use of 'old' antibiotics with good efficacy against MDR organisms

Polymyxins have been marketed since 1950s. Two polymyxins are commercially available, polymyxin B and polymyxin E (colistin). Polymyxin B does not have a prodrug and is administered in the form of its active microbiological agent. Colistin is a cationic peptide and exhibits concentration-dependent activity against many MDR organisms. Until recently, its use was negligible due to nephro- and neurotoxicity concerns. However, increasing resistance rates among gram-negative pathogens against which colistin is very active has resurrected the use of this old drug.

Colistin is administered as prodrug (colistin methanesulfonate [CMS]), which *in vivo* slowly is converted to active compound colistin. In critically ill adults, it will take 2–3 days before the steady state is achieved suggesting the need of loading doses [119]. Both prodrug and active compound have different pathways of elimination. More specifically, colistin has longer elimination half-life and, in contrast to CMS, does not undergo extensive renal elimination. Thus, its concentration in bloodstream is much lower than previously reported [120]. Recent PK/PD studies together with extensive popPK analysis and modeling in adult patients have demonstrated that in severe infections a loading dose of 9 MU (720 mg or 10 mg/kg in a 70-kg patient) of CMS should be followed by the 9 MU fractioned twice-daily maintenance dose to achieve maximum efficacy [119,121].

In children, colistin has been used mostly in patients with CF. In non-CF patients, doses of 50,000–80,000 IU/kg (4–6 mg/kg CMS) divided into two- to four-times a day with no loading dose have been used [122–124]. The dose of colistin that in children will achieve similar exposure to adults (fAUC/MIC 50–65 or greater) has not yet been defined, but it is likely that similar to adults, a loading dose followed by high maintenance dose is required when treating severe infections caused by MDR organisms.

One concern with the use of higher doses of colistin is the potential nephrotoxicity and/or neurotoxicity. In two pediatric retrospective studies using currently recommended dosing regimen, nephrotoxicity ranged between 10 and 22% [122,124] and neurotoxicity was reported in 4 patients out of 92. These figures are similar to those reported in adults by using the above-described high dose of colistin [125]. Thus, current limited data in adults suggest that high doses of colistin are relatively effective with acceptable and reversible nephrotoxicity in severely ill patients. It is important to note that in clinical settings, colistin is often given in combination with other antibiotics [122], although a clear benefit of combination therapy has not been demonstrated yet.

Fosfomycin is a cell-wall inhibitor with time-dependent bacterial killing. In therapeutically relevant concentrations, fosfomycin exerts excellent *in vitro* bactericidal activity against a wide spectrum of gram-positive and gram-negative bacteria including MRSA, methicillin-resistant *S. epidermidis*, PRSP, VRE, ESBL-producing enterobacteria and the majority of *P. aeruginosa* strains [126]. Even in regions where fosfomycin is frequently prescribed, the emergence of resistance to fosfomycin is a minor problem [127–129]. It is important to note that this antibiotic is currently not utilized in bioindustry and animal husbandry. Intravenous fosfomycin is generally well tolerated and its adverse effects (mostly gastrointestinal symptoms and phlebitis) do not necessitate treatment discontinuation. Furthermore, fosfomycin exerts negligible protein binding [130] and penetrates well into the interstitial space fluid of tissues [131,132]. Intravenous fosfomycin has been in clinical use for almost four decades in Japan, some European countries and in South America. However, the current dosing recommendations vary from 100 to 400 mg/kg/day divided into 2–3 doses regardless of age; the highest end of dosing band is recommended for severe infections [133]. No dosing recommendations are given for children with renal impairment. Available PK studies were recently reviewed and the  $T > MIC$  values for currently recommended doses were recalculated by Traunmuller *et al.* [133]. The authors concluded that for achieving  $T > MIC$  target of 40–70%, the current dosing strategies are insufficient in children aged 1–12 years, if pathogens with MIC of 32 mg/l are suspected and subjects have normal renal function. Because of the time-dependent PD properties, fosfomycin needs to be given every 6–8 h except of premature neonates for whom the 12 hourly dosing intervals are sufficient. Further studies should clarify the PK of fosfomycin in children at any age and at different stages of renal impairment to identify the most appropriate doses for children.

### Combination versus monotherapy of antibiotics

In desperate situations (e.g., sepsis caused by MDR organisms), combination antibiotics with different mechanisms of action is commonly used despite the controversial evidence. The benefits of combination therapy include broader antibacterial coverage, enhanced efficacy through the synergistic effects between different antibiotics and prevention of resistance development. The pros and cons of antibiotic combinations are thoroughly reviewed elsewhere [134].

*In vitro* several antibiotic combinations act synergistically even if the microorganism is resistant to both agents in the combination (TABLE 1).

Still, *in vitro* synergy appears to be variably present, is strain- and inoculum size-dependent and varies in different antibiotic combinations [135]. One of the combinations that has shown synergistic effect *in vitro* and in animal models against MDR-GN organisms, especially *A. baumannii*, is colistin plus a glycopeptide (vancomycin or teicoplanin), due to the activity of glycopeptides on the cell wall after overcoming the outer membrane. This combination could potentially be used in



**Table 1. Selected antibiotic combinations that act synergistically against multidrug-resistant microorganisms *in vitro*.**

Antibiotic	Microorganisms	Ref.
Colistin with		
aztreonam	VIM and NDM <i>Klebsiella pneumoniae</i>	[165]
fosfomicin	VIM and NDM <i>K. pneumoniae</i>	[165]
meropenem	VIM and NDM <i>K. pneumoniae</i> ; CR <i>K. pneumoniae</i>	[165,166]
rifampicin	VIM and NDM <i>K. pneumoniae</i>	[165]
vancomycin	MDR <i>Acinetobacter baumannii</i>	[136]
β-Lactam with aminoglycoside		
oxacillin + gentamicin	MRSE	[135]
Tigecycline with		
rifampicin	CR <i>K. pneumoniae</i>	[167]
fosfomicin	CR <i>K. pneumoniae</i>	[168]
colistin	CR <i>Enterobacteriaceae</i> (except <i>Serratia marcescens</i> )	[169]
β-Lactam with other		
doripenem + fosfomicin	MRSA, MDR <i>Escherichia coli</i> and MDR <i>K. pneumoniae</i>	[170]

CR: Carbapenem-resistant; MDR: Multidrug-resistant; MRSA: Methicillin-resistant *Staphylococcus aureus*; MRSE: Methicillin-resistant *Staphylococcus epidermidis*; NDM: New Delhi metallo-β-lactamase; VIM: VIM-type metallo-β-lactamase.

colistin-resistant strains to prevent further development of colistin resistance but the data are highly experimental thus far [136,137].

The best established combination today is β-lactam plus AG. In the treatment of sepsis, AG are never used alone, although successful monotherapy has been reported [69].

Despite the theoretical grounds and *in vitro* findings, the supporting clinical data are neither overwhelming nor definitive. Meta-analyses that have been conducted exclusively on RCT in adults demonstrate no difference in clinical outcomes or mortality between mono- and combined therapy, but there are well-documented increased toxicities with the combination therapy [138]. Studies in children point to the same direction. In a retrospective analysis comparing β-lactam monotherapy with combination therapy in children with gram-negative bacteremia, no difference in mortality was found but similarly to

adults combination therapy resulted in doubling odds of nephrotoxicity (OR: 2.15; 95% CI: 2.09–2.21) [139]. However, in contrast to earlier studies, a more recent retrospective study including 226 matching pairs of children with gram-negative bacteremia treated with a β-lactam alone or in combination with AG demonstrated a survival benefit of empirical combination therapy in patients infected with MDR organisms (OR: 0.70; 95% CI: 0.51–0.84), suggesting the benefits of combination therapy when antibiotic-resistant organisms are suspected [140].

It is still important to note that most of the analyzed studies have included highly variable patient populations, employed a range of antibiotics and/or their combinations and did not have sufficient power to analyze patients infected with resistant or difficult-to-treat microorganisms separately. The meta-analyses also showed that monotherapy with broad-spectrum β-lactam is more efficacious than the combination of an older β-lactam with AG but there are very little comparative studies on combining new broad-spectrum β-lactams with AG [134,138]. An RCT comparing combination of ampicillin or cefotaxime with gentamicin to meropenem monotherapy in neonatal sepsis is ongoing and results are awaited in 2015 [141].

As mentioned above in clinical settings colistin is rarely given as monotherapy. Commonly it is combined with an antibiotic to which the isolate is resistant (e.g., a carbapenem), to improve the outcomes of colistin monotherapy. Paul *et al.* [142] plotted the results of all-cause mortality in 12 retrospective cohort studies or case series, 2 prospective observational studies and 2 RCTs for colistin mono- versus combination therapy in a forest plot, sub-grouped by the type of combination regimen (unadjusted results in the observational studies) and found no differences between two study regimens against CR gram-negative bacteria. Presently, an international RCT comparing colistin/carbapenem combination therapy to colistin monotherapy for invasive infections caused by CR gram-negative bacteria [143,144] is ongoing and hopefully the evidence, at least in adults will emerge in the near future. The results then could be extrapolated to pediatric population.

Although combination therapy has not been proven better than monotherapy in general, a number of studies have suggested that in severely ill or septic patients there is a survival benefit of combining antibiotics in patients with *K. pneumoniae* or *Enterobacter* bacteremia [145] and those in septic shock [146]. However, in a meta-analysis of 64 RCTs comprising 7568 patients, comparing β-lactam and AG combination therapy with β-lactam monotherapy for severe infections no difference in mortality between the treatment groups was observed (RR: 0.90; 95% CI: 0.77–1.06) [147]. Thus, further studies with new and broad-spectrum antibiotics need to be performed to conclusively demonstrate that combination therapy is better and as well tolerated as monotherapy in patients with severe sepsis or septic shock.

### Monitoring mucosal colonization

There is sufficient amount of evidence that opportunistic microorganisms causing late-onset sepsis in neonates at first colonize

**Table 2. Treatment option for sepsis caused by multidrug-resistant microorganisms.**

		First-line treatment	Potential for the second-line treatment
<i>Staphylococcus aureus</i>	MRSA	Vancomycin	Vancomycin prolonged infusion Linezolid <sup>†</sup> Clindamycin <sup>‡</sup> Ceftaroline Daptomycin
<i>Staphylococcus epidermidis</i>	MRSE	Vancomycin	Vancomycin prolonged infusion Linezolid Oxacillin + gentamicin Oxacillin + rifampin
VRE		Linezolid	Daptomycin
<i>Streptococcus pneumoniae</i>	PRSP	High-dose penicillin G <sup>†</sup> third-generation cephalosporins	Third-generation cephalosporins + vancomycin
<i>Enterobacteriaceae</i>	ESBL	Meropenem Imipenem/cilastatin	Tigecycline Colistin + aminoglycoside Fluoroquinolone TMP/SMX
	AmpC	Meropenem Cefepime	Tigecycline Colistin + aminoglycoside
	KPC	Colistin + aminoglycoside Fosfomycin	High dose meropenem+ colistin OR aminoglycoside OR fluoroquinolone Tigecycline
<i>Pseudomonas aeruginosa</i>	KPC	Colistin + aminoglycoside Fosfomycin	Colistin+ fluoroquinolone
<i>Acinetobacter baumannii</i>	MDR	Ampicillin sulbactam Tigecycline	Colistin + fosfomycin Colistin + tigecyclin Tigecyclin + aminoglycoside High dose meropenem + aminoglycoside OR fluoroquinolone OR colistin

<sup>†</sup>Not suitable if meningitis is suspected.

<sup>‡</sup>Not suitable for endovascular infections.

ESBL: Extended-spectrum  $\beta$ -lactamases; KPC: *Klebsiella pneumoniae* carbapenemase; MDR: Multidrug-resistant;

MRSA: Methicillin-resistant *Staphylococcus aureus*; MRSE: Methicillin-resistant *Staphylococcus epidermidis*; PRSP: Penicillin-resistant *Streptococcus pneumoniae*;

mucosal surfaces of the GI tract and/or nasopharynx [148–152]. Thus, it would be logical to use monitoring of mucosal cultures in selecting empiric therapy for sepsis. Still, studies conducted in neonatal intensive care units indicate that non-selective monitoring of mucosal cultures is labor intensive, time consuming and costly and has suboptimal sensitivity and specificity in predicting neonatal late-onset sepsis [149,153,154]. This does not mean that monitoring of mucosal cultures should be totally abandoned. If targeted to a specific MDR organism, the active continuous surveillance combined with appropriate isolation of affected patients could significantly reduce the number of colonized patients with MDR-GN organisms in neonatal intensive care unit [155,156]. Whether the reduction in colonization will result in reduction of infection rate will be studied in the large nationwide program in Germany introduced in 2012 [157].

### Treatment recommendations

Emerging resistance together with the increasing role of immunocompromise and previous exposure to toxic therapies (i.e., chemotherapy) warrants a well-tailored approach in the

antibacterial treatment of pediatric sepsis. Treatment recommendations by pathogen and resistance mechanism are summed up in TABLE 2, the final choice remaining to be guided by the source of infection and local resistance data. Due to the lack of pediatric data, the large majority of these recommendations are based on *in vitro* or experimental data or studies conducted in adults.

In children with high risk of resistant gram-negative pathogens, a primary choice covering broad antimicrobial spectrum such as a fourth-generation cephalosporin or a carbapenem (meropenem) should be preferred [158]. Because of growing clinical data demonstrating therapeutic failure of third-generation cephalosporins for *Enterobacter* species, these agents are not recommended for invasive *Enterobacter* infections [158]. Broad-spectrum  $\beta$ -lactam/ $\beta$ -lactamase inhibitor combinations may be considered as an alternative. A *post hoc* analysis of six prospective cohorts evaluating broad-spectrum  $\beta$ -lactam- $\beta$  lactamase inhibitor (piperacillin-tazobactam or amoxicillin clavulanate) versus carbapenems in the treatment of adult ESBL *E. coli* bacteremia found similar mortality rates and length of hospital stay in both groups [159]. Increased clinical and

microbiological failure and mortality rates with cefepime compared to a carbapenem have been found in an adult RCT of ESBL bacteremia [158]. Increase in cefepime MIC with an increase in inoculum size makes it a less reliable option, especially for infections with high bacterial burden [158]. However, in confirmed AmpC-producing *Enterobacteriaceae* bacteremia, hospital-acquired pneumonia or intra-abdominal infections with adequate source control, cefepime has been found equally effective compared with meropenem [160]. In general, combination therapy has not been proven advantageous over monotherapy but may be considered in situations like septic shock or high likelihood of MDR-GN infection.

Bacteremia caused by PRSP could still be treated with penicillin G bearing in mind that higher doses and more frequent administration or prolonged infusion should be used to overcome increased MICs. However, penicillin G (even in high doses) is suboptimal in patients with pneumococcal meningitis as penicillin poorly penetrates through blood–brain barrier. In meningitis, the combination of third-generation cephalosporins with vancomycin is the first choice.

Vancomycin is the first choice for the treatment of bacteremia and infective endocarditis caused by staphylococci. Data regarding the safety and efficacy of alternative agents in children are still limited, although new agents might be an option. Clindamycin and linezolid as bacteriostatic agents are alternative treatments for non-endovascular infections. The clinical evidence of combinations therapy (vancomycin + gentamicin, vancomycin + rifampicin, oxacillin + gentamicin) in staphylococcal infections caused by methicillin-resistant organisms is still very limited [161].

Prolonged or continuous infusion of time-dependent antibiotics in the treatment of infections due to pathogens with increased MIC values is supported by *in vitro* data and PK/PD modeling studies. Based on existing clinical evidence, its routine use cannot be recommended. When applied, loading dose should be used to achieve timely bactericidal concentrations. The role of  $\beta$ -lactam TDM remains to be established.

### Expert commentary

Resistance of microorganisms to antibiotics is increasingly important, particularly in children with added comorbidities undergoing frequent hospitalizations and repeated antibiotic courses. The widespread antibiotic resistance is most alarming in the hospital setting (nosocomial infections); however, patients infected with MDR bacteria could be admitted from community settings as well.

Treating children with sepsis caused by the MDR organisms pose many challenges for physicians. The most important is the lack of data. Most RCTs on antibiotic treatment has been conducted in adults so far and even then the studies have been too small to draw specific recommendations for patients with MDR organisms or critically ill. Considering the small number of children with sepsis caused by MDR organisms, it is unlikely that RCT are feasible. Furthermore, they may not be needed, provided that with currently recommended doses,

antibiotic exposure in children and adults is similar. Therefore, using PK/PD approach and extrapolating efficacy data from adult studies will likely be the direction for the future.

It is of utmost importance that the PK studies in children be conducted sooner than later as it has been clearly demonstrated that due to immaturity of drug-eliminating organs, the PK properties of all medicines including antibiotics differ significantly between children and adults and also between various pediatric age groups. Several recommendations in this review are based on adult data. For example, if high doses are shown to be more efficacious in adults, similar suggestions were made for children as well, despite the fact that there are no data.

When making treatment recommendations for specific antibiotic-resistant microorganisms, several sources (e.g., PK safety and efficacy studies in adults, *in vitro* susceptibility data, PK/PD modeling and experimental models) were considered by carefully weighing pros and cons of the recommended regimen. We believe that suggestions made by us could be safely used in children, but appreciate that extrapolated and modeled data have limitations. We believe that using PK/PD modeling allows fast generation of pediatric data and is often the only option. However, the modeling is likely sufficient in making efficacy claims but we are not aware of any antibiotic PK/PD approach that also accounts for safety concerns. The latter should be considered, as most model-based dosing recalculations recommend higher doses that are currently in use.

### Five-year view

Although several pharmaceutical companies have departed from antibiotic development, few new agents with the potential to cover MDR microorganisms (mostly gram-positives) are in clinical development. For some of them, clinical trials in children are planned or are already ongoing (e.g., ceftazidime/avibactam, tazobactam/ceftolozane, tedizolid) [162]. There are antibiotics approved for adults for which pediatric investigational plans are agreed and pediatric data should become available soon. This all will broaden our options for management of septic patients infected with MDR organisms.

Although attrition rate of monoclonal antibodies in treatment of bacterial infections has been high thus far, the search for new opportunities is continuing. Growing number of biotechnology companies are engaged in the development of monoclonal antibodies or their cocktails for prevention and/or adjunctive treatment of infections caused by MDR microorganisms (e.g., *S. aureus*, *P. aeruginosa*). Some of these monoclonal antibodies have entered into early phases of clinical development [163].

It is also hoped that the diagnostic possibilities will improve so that the patients infected with MDR organisms could be rapidly identified. This would then allow immediate initiation of appropriate therapy and isolation of infected patients in order to prevent further spread of MDR organisms. New diagnostic techniques like matrix-assisted laser desorption/ionization-time of flight allowing rapid and cheap detection of specific antibiotic resistance mechanisms in addition to identification of microorganisms are already introduced to clinical practice [164].

With the further development of medical devices, the treatment of critically ill patients becomes more individualized; equipment for bedside TDM is already under development.

Last but not least, several international studies will broaden our understanding of the prevalence of antibiotic resistance worldwide and enable knowledge transfer on the prevention and rational antibiotic use from one country to the other.

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#### Key issues

- Efficacy data on the treatment of sepsis caused by multidrug-resistant (MDR) organisms in children are largely extrapolated from adult studies, as evidence-based pediatric studies are very limited. Pharmacokinetic/pharmacodynamic studies can partly overcome existing gaps.
- The number of new antibiotics for treatment of MDR infections in children is still low.
- Old agents (i.e., colistin, fosfomycin) could be potentially used after appropriate dosing regimen for all pediatric age groups have been defined.
- Advanced generation  $\beta$ -lactams for MDR gram-negative organisms and vancomycin for methicillin-resistant *Staphylococcus aureus*/methicillin-resistant *S. epidermidis* remains the cornerstone of therapy.
- Prolonged or continuous infusion of time-dependent antibiotics for pathogens with increased MICs is supported by the pharmacokinetic/pharmacodynamic modeling studies, but existing clinical evidence is still too limited to recommend its routine use.
- When prolonged infusion is applied, a loading dose should be used to achieve timely bactericidal concentrations.
- ODD doses of aminoglycosides have been safely used in neonates and children with sepsis.
- For vancomycin and aminoglycosides, high inter-individual and inter-microbial variability mandates the use of therapeutic drug monitoring to ensure safety and efficacy. The role of  $\beta$ -lactam therapeutic drug monitoring remains to be established.
- Combination therapy should be reserved for situations with high risk of resistance and/or severe disease. When considered, increased adverse event rates compared to monotherapy need to be borne in mind.

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