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To cite this article: Alexandre P. Zavascki, Brandon O. Klee & Jürgen B. Bulitta (2017): Aminoglycosides against carbapenem-resistant Enterobacteriaceae in the critically ill: the pitfalls of aminoglycoside susceptibility, Expert Review of Anti-infective Therapy, DOI: 10.1080/14787210.2017.1316193

To link to this article: http://dx.doi.org/10.1080/14787210.2017.1316193

Accepted author version posted online: 04 Apr 2017.
Published online: 17 Apr 2017.

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Aminoglycosides against carbapenem-resistant Enterobacteriaceae in the critically ill: the pitfalls of aminoglycoside susceptibility

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ABSTRACT

Introduction: The emergence of carbapenem-resistant Enterobacteriaceae (CRE) has brought aminoglycosides to the forefront since an aminoglycoside may be the only antimicrobial to which CRE isolates show in vitro susceptibility. The appropriateness of aminoglycoside-based therapies for severe infections by CRE is discussed considering the current breakpoints and recent pharmacokinetic (PK) studies in critically ill patients.

Areas covered: Many aminoglycoside-susceptible CRE isolates present minimal inhibitory concentrations (MICs) at or slightly below the breakpoint of amikacin or gentamicin. However, recent PK studies with these aminoglycosides in critically ill have invariably shown that the PK/pharmacodynamic (PD) target is very unlikely attained even when high doses are administered, if the MICs are near the breakpoint.

Expert commentary: While new antimicrobials are not widely available, the authors forecast an increasing use of aminoglycosides as backbone antibiotics against CRE isolates. However, the altered PK of aminoglycosides in critically ill patients severely impairs their predicted efficacy in these patients. Aminoglycoside breakpoints may hide 'aminoglycoside-susceptible' CRE isolates for that aminoglycoside will unlikely be effective if used in monotherapy. Therefore, these breakpoints may need to be revised due to the increasing use of aminoglycosides as backbone antibiotics to treat severe infections by CRE isolates in critically ill patients.

1. Introduction

The worldwide emergence of carbapenem-resistant Enterobacteriaceae (CRE), mostly driven by the dissemination of carbapenemase-producing isolates, has caused a substantial public health problem, which is exacerbated by vanishingly few therapeutic options remaining [1]. The old polymyxin antibiotics, colistin and polymyxin B, have usually been the backbone agents against CRE isolates in combination schemes [2]. Many of these isolates are also susceptible to aminoglycosides, usually amikacin or gentamicin, depending on the presence of specific plasmid-borne genes encoding aminoglycoside-modifying enzymes. The latter confer resistance to a given aminoglycoside but may spare other members of this class [3,4]. Occasionally, susceptibility to both aminoglycosides is seen in some CRE isolates. Thus, aminoglycosides have sometimes been prescribed as a second agent with in vitro activity in combination schemes with polymyxins. However, and most importantly, resistance to polymyxins has been strikingly high among Klebsiella pneumoniae carbapenemase (KPC)-producing Klebsiella pneumoniae isolates in some countries [5–7]. Consequently, we forecast an increasing use of the old aminoglycosides as a backbone agent for infections by CRE isolates.

Aminoglycosides have been rarely prescribed as monotherapy for severe infections by gram-negative bacteria due to the lower clinical efficacy [8] and extensive emergence of resistance [9]. Moreover, published clinical data of these agents used as backbone antibiotics against CRE isolates are scarce, especially in critically ill patients. It is therefore important to reappraise our current practice based on pharmacokinetic (PK) and PK/pharmacodynamic (PD) principles. Indeed, currently, PK and PK/PD knowledge is likely the best available evidence supporting the rational use of aminoglycosides against infections by CRE. In this article, we discuss the therapeutic options and perspectives for treatment of infections by ‘aminoglycoside-susceptible’ CRE and which factors need to be considered for these infections in critically ill patients, with a special focus on PK and PK/PD of these antibiotics and their relation to current breakpoints. Some of the general considerations in this review may be applied to the therapeutic management of infections caused by other gram-negative bacteria; additionally, specific recommendations are provided based on studies performed with CRE isolates and should be considered accordingly.
2. Aminoglycoside-susceptible CRE isolates

In fact, susceptibility rates of CRE (most data come from KPC-producing \textit{K. pneumoniae}) for amikacin and gentamicin are encouraging, although tobramycin resistance rates tend to be higher \cite{3,4,7,10}. A more thorough evaluation of the minimal inhibitory concentrations (MICs) for CRE isolates, which have been sporadically reported, indicates that a remarkable proportion of these MICs are slightly below or at the susceptibility breakpoints \cite{3,11-16}. Considering the clinical breakpoints of aminoglycoside, in particular the high Clinical and Laboratory Standards Institute (CLSI) breakpoints \cite{17,18}, the ‘susceptible’ category may host isolates with quite different phenotypes. For example, two isolates with amikacin MICs of 1 and 16 mg/L will both be considered ‘susceptible,’ despite the substantially different bacterial killing expected to be caused by amikacin treatment (i.e. monotherapy).

As we will show below, the ‘aminoglycoside-susceptible’ label must be interpreted with caution if aminoglycosides are being considered as the main antibiotic in a combination against a CRE isolate. This is particularly important, since clinicians are used to prescribe standard (i.e. low) clinical doses of aminoglycosides. If an MIC is near the susceptibility breakpoint, a low dose will likely be inappropriate, particularly in severe infections and immunocompromised patients when successful treatment mostly relies on the efficacy of antimicrobial therapy. Therefore, for treatment of CRE infections in critically ill patients, one size (i.e. dose) definitely does not fit all patients.

Aminoglycosides have been used for decades, mostly as ‘adjuvant’ antibiotics, i.e. in combinations to enhance the efficacy of a second drug – usually a β-lactam. Therefore, their pharmacological properties need to be considered carefully when used as the cornerstone agent in combination schemes, even if aminoglycosides are one of or the only remaining option for severe CRE infections in critically ill patients.

3. PK/PD of aminoglycosides

At high concentrations, aminoglycosides can achieve very rapid bacterial killing \cite{19,20}. Both antibiotic peak concentrations as well as total aminoglycoside exposure contribute to the efficacy of aminoglycosides \cite{17,21,22}. The PK/PD indices that best predict the activity of aminoglycosides in monotherapy are the unbound area under the plasma concentration–time curve divided by the MIC (\(\text{fAUC/MIC}\)) and the unbound peak concentration by MIC ratio (\(\text{faC}_{\text{max}}/\text{MIC}\)) \cite{17,21,23}. Protein binding of aminoglycosides is very low. A \(\text{faC}_{\text{max}}/\text{MIC}\) ratio of at least 8–10 is used as PK/PD target to predict efficacy of aminoglycosides \cite{21}.

From a clinical perspective, the distinction between \(\text{faC}_{\text{max}}/\text{MIC}\) and \(\text{fAUC/MIC}\) as the PK/PD index for aminoglycosides has limited practical impact because these PK/PD indices are highly correlated if once-daily dosing is used. There are important clinical benefits of once-daily compared to three-times daily dosing, such as lower renal toxicity \cite{24} and more rapid initial bacterial killing (including potential killing of preexisting resistant mutants) \cite{19,20,23,25}. In addition, peak concentrations are easy to monitor and allow for a straightforward interpretation of aminoglycoside serum concentrations.

4. Recent PK data

Recent PK studies, especially with amikacin, have been invariably demonstrating that it is difficult to obtain effective peak concentrations, even at doses higher than those approved clinically for amikacin (15–20 mg/kg) and gentamicin (3–5 mg/kg; Table 1) \cite{26-35}. Given these PK results, it is difficult to achieve the PK/PD target even for isolates that have a ‘susceptible MIC’ at the breakpoint as defined by European Committee on Antimicrobial Susceptibility Testing

\begin{table}
\centering
\caption{Summary of recent pharmacokinetic studies with amikacin and gentamicin.}
\begin{tabular}{llllll}
\hline
Aminoglycoside/author, year & \multicolumn{1}{c}{No. of patients or aminoglycoside courses} & Patient population & First dose, mg/kg\textsuperscript{a} & Duration of infusion, min & \text{C}_{\text{max}}\textsuperscript{b}, mg/L \\
\hline
\textbf{Amikacin} & & & & & \\
Brasseur, 2016 \cite{26} & 11 & Critically ill & 29 (25–37)\textsuperscript{c} & 30 & 77 (66–89) \\
Roger, 2016 \cite{27} & 47 & Critically ill & 29.6 ± 3.3\textsuperscript{b} & 30 & 75.8 ± 24.5 \\
White, 2015 \cite{28} & 73 & Hospitalized & 28.0 ± 8.47 & 60 & 101 ± 49.4 \\
Roger, 2015 \cite{29} & 66 & Critically ill & 22.6 ± 6.9 & 30 & 50.9 ± 19.1 \\
Blackburn, 2015 \cite{30} & 24 & Critically ill with hematological malignancies & 13.8 ± ND\textsuperscript{b} & 60 & 33.5 ± 15.8 \\
De Montmollin, 2014 \cite{31} & 181 & Critically ill & 25 (24.6–25.5)\textsuperscript{a} & 30 & 69 (54.9–84.4)\textsuperscript{a} \\
Galvez, 2011 \cite{32} & 99 & Critically ill & 15 & 30 & 35.2 ± 9.4 \\
 & & & 25 & & 57.4 ± 9.8 \\
 & & & 30 & & 72.1 ± 18.4 \\
Taccone, 2010 \cite{33} & 74 & Critically ill & 25 & 30 & 91.7 (73.1–113)\textsuperscript{a} \\
\textbf{Gentamicin} & & & & & \\
Brasseur, 2016 \cite{26} & 3 & Critically ill & 10 & 30 & 21 \ & & & 11 & & 27 \\
 & & & 18 & & 39 \\
Roger, 2016 \cite{29} & 16 & Critically ill & 7.8 ± 1.3\textsuperscript{b} & 30 & 20.4 ± 4.6 \\
Roger, 2015 \cite{29,35} & 24 & Critically ill & 6.6 ± 2.3 & 30 & 15.7 ± 7.3 \\
\hline
\end{tabular}

\textsuperscript{a}Doses calculated by actual body weight.

\textsuperscript{b}Data obtained from samples collected at the end or 30–60 min after the end of infusion.

\textsuperscript{c}Median (range).

\textsuperscript{d}Doses calculated by actual body weight with adjustments for obese patients.

\textsuperscript{e}Median (interquartile range).

ND: not described.
has been reported by Shields and colleagues [38]. The authors analyzed 33 patients (32 treated with gentamicin and 1 with amikacin). Most patients received a second antibiotic in combination that had no in vitro susceptibility for the infecting pathogen. The clinical success rate for aminoglycoside-based combination therapy was 54% (with 14- and 30-day survival rates of 78 and 70%, respectively). However, this study was not well suited to evaluate the efficacy of aminoglycoside monotherapy against CRE, since 70% of patients received a combination with another antimicrobial (all combinations included a carbapenem). In addition, doses were not reported in the study. Finally, in the 32 patients treated with gentamicin, MICs were relatively low, which may not be extrapolated to all CRE isolates, with 1 mg/L in 11 patients and 0.5 mg/L or less in 16 patients. Only three patients had an MIC of 2 mg/L and one patient had an MIC of 4 mg/L, the latter resulting in treatment failure and death [38]. Only one patient was treated with amikacin and had an MIC of 16 mg/L which resulted in treatment failure and death.

5. Clinical experience with aminoglycosides as backbone agents against severe infections by CRE

There are still only a few published experiences detailing treatment with aminoglycosides as the backbone agent against CRE. In addition, these studies are not limited to critically ill patients, so extrapolation of the overall results must be done with caution. Aminoglycoside-based therapies are likely to become more common for the treatment of polymyxin-resistant CRE isolates [37,38].

The first study reported the results of 50 patients with colistin-resistant KPC-producing K. pneumoniae sepsis in which 29 patients (58%) received a regimen containing gentamicin at usual doses (4–5 mg/kg/day); doses were further adjusted to obtain a peak concentration of 15 to 20 mg/L [37]. Thirty-day mortality was significantly lower in patients treated with gentamicin-containing regimens (20.7% versus 61.9%, \( p = 0.02 \)). Eight patients received gentamicin in monotherapy and the mortality was 12.5% (1 patient). Twenty-one patients received gentamicin in combination with tigecycline and mortality was 23.8% (5 patients). It was interesting that among patients treated with gentamicin, 13 infected by isolates with a gentamicin MIC ≤2 mg/L tended to have a lower mortality (7.7%, 1 patient) than the 16 patients infected by isolates with an MIC of 4 mg/L (31.2%, 5 patients, \( p = 0.18 \)) [16]. While the number of patients is small, these results are consistent with the PK/PD predictions for aminoglycosides. The mean peak concentration of gentamicin obtained in these patients was 18.2 ± 2.6 mg/L (equivalent to a mean \( \text{C}_{\text{max}}/\text{MIC} \) of approximately 9.1 for a MIC of 2 mg/L) [37].

Another study on aminoglycosides against carbapenem-resistant K. pneumoniae has been reported by Shields and colleagues [38]. The authors analyzed 33 patients (32
A recent cohort study has shown that only 12% of 562 patients treated with aminoglycosides for at least 5 days presented acute kidney injury (AKI) as defined by the modified Risk, Injury, Failure, Loss, and End-stage kidney disease criteria [44]; this is encouraging for situations when the use of an aminoglycoside is required for a longer period. Another recent study has found a rate of 17% of AKI as defined by Kidney Disease: Improving Global Outcomes (KDIGO) criteria among 278 elderly patients with a mean age of 74 years [48]. These rates were higher in patients with septic shock (33%). Noteworthy, the authors could not find any association between peak or trough and the incidence of AKI. However, AKI was significantly more common in patients receiving more than 10 days of therapy [48].

Short courses are however not always possible in some severe infections and the risk/benefit ratio should be judiciously considered, especially if no alternative therapeutic option is available.

Regarding ototoxicity, either vestibular or cochlear damage has been associated with prolonged exposure to aminoglycosides and has been reported to be largely dependent on specific individual vulnerability [47,49]. The impact of high aminoglycoside doses on ototoxicity, however, warrants further investigations.

7. Combination regimens

An aminoglycoside offers the benefit that it may disrupt and thereby permeabilize the outer membrane of gram-negative bacteria [19,20,25]. This likely enhances the target site penetration of the antibiotic used in combination and thereby leads to synergistic bacterial killing (Figure 1). Additionally, aminoglycosides have been shown to lead to decreased β-lactamase expression; this synergy mechanism contributed to resistance suppression by aminoglycoside plus cefepime combination regimens in Pseudomonas aeruginosa [50].

Only a small number of in vitro time–kill studies systematically assessed aminoglycoside combinations against CRE. Except for one experimental study [51], no in vitro studies are available for infection models with a high bacterial density that may mirror more severe infections.

Hirsch et al. [51] assessed two-drug combinations of amikacin, doripenem, rifampicin, and levofloxacin against one KPC-2- and one KPC-3-producing K. pneumoniae isolate. The first isolate had amikacin/doripenem MICs of 64/16 mg/L and the second isolate of 32/32 mg/L. Amikacin plus doripenem was the most active combination in vitro. In a high-inoculum neutropenic mouse pneumonia model, amikacin monotherapy and the amikacin plus doripenem combination yielded 0.5 to 1 log10 bacterial killing against the KPC-3-producing isolate, but not against the KPC-2 producer. Importantly, this combination provided a significantly improved mouse survival for both isolates.

Le et al. [52] studied four carbapenem-resistant K. pneumoniae isolates (carrying a KPC-3 β-lactamase) with an amikacin MIC of 32 mg/L in vitro. Amikacin plus meropenem yielded 1.7 to 3.6 log10 bacterial killing at 24 h (relative to the initial inoculum). Amikacin plus imipenem achieved 0.1 to 3.5 log10 killing at this time point.

Tang et al. [53] evaluated 13 genetically different KPC-producing K. pneumoniae isolates with an amikacin MIC of <0.5 and 16 mg/L for gentamicin. Amikacin or gentamicin combined with a second protein synthesis inhibitor (i.e. tigecycline or doxycycline) yielded consistently better activity in all isolates (for amikacin) or the vast majority of isolates (for gentamicin) compared to the most active monotherapy. This includes combinations with clinically relevant tigecycline concentrations of 1 to 2 mg/L; the tested doxycycline concentrations were higher. Similarly, at least 3 log10 bacterial killing and synergy were observed for most of the isolates and combinations tested.

Overall, the few available in vitro time–kill studies on aminoglycoside combinations against CRE yielded promising results, especially if the aminoglycoside MICs were in the susceptible range. Synergistic bacterial killing and prolonged mouse survival were, however, also found for two

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Figure 1. Mechanisms of aminoglycoside action (i.e. interference with protein synthesis and permeabilizing the outer membrane). Inhibition of protein synthesis may lead to decreased expression of β-lactamase enzymes. Permeabilizing the outer membrane likely enhances the target site penetration of a second antibiotic (e.g. a β-lactam). Both mechanisms may therefore yield synergy in aminoglycoside-based combination regimens.
amikacin-resistant K. pneumoniae isolates [51]. These studies showed synergy of aminoglycoside (usually amikacin or gentamicin) plus carbapenem combinations. Aminoglycoside combinations with a second protein synthesis inhibitor (i.e. tigecycline or doxycycline) were active against some KPC-producing K. pneumoniae isolates.

We believe that whenever an aminoglycoside is considered as the backbone antibiotic against aminoglycoside-susceptible CRE isolates, it should be combined with a second antibiotic that has a susceptible MIC, if possible.

Beyond PK/PD considerations, observational studies have suggested that a combination of two agents with in vitro activity against CRE isolates results in lower mortality compared to that of monotherapy [2,54,55], although these studies have not specifically addressed aminoglycoside-containing schemes. Furthermore, such combination therapies are likely required to kill or prevent amplification of the (small) subpopulation of aminoglycoside-resistant bacteria that are most likely present before initiation of antibiotic therapy, especially for severe infections [25].

When a second antimicrobial with in vitro susceptibility is not available, the few available nonclinical studies consistently suggest that aminoglycoside plus carbapenem combinations can provide extensive and synergistic bacterial killing against CRE, despite carbapenem resistance [16,51,52]. Importantly, even against two double-resistant K. pneumoniae isolates, amikacin plus doripenem significantly prolonged mouse survival in a high inoculum lung infection model [51]. Other aminoglycoside combinations (e.g. those with tigecycline) may also be beneficial. Overall, it is clear that more systematic in vitro and animal infection model studies are needed to rationally optimize these combinations and dosage regimens for translation to critically ill patients.

8. Conclusions

In summary, the susceptible label of aminoglycosides, especially based on the CLSI breakpoints, may contain isolates with relatively high MICs that may preclude the effective use of aminoglycosides in monotherapy. Recent PK studies have shown that even with high aminoglycoside doses given once daily, most patients infected by aminoglycoside-susceptible CRE with MICs slightly below or at the breakpoint will not achieve the PK/PD target for aminoglycosides in critically ill patients. This may have serious clinical implications when aminoglycosides are considered either in monotherapy or as the backbone agent in combination schemes for severe infections. High-dose aminoglycoside in rationally optimized combination therapies seems to be the best strategy when these drugs are considered for the treatment of CRE infections in critically ill patients. Aminoglycoside breakpoints should be revised in the context of an increasing use of these antimicrobials against carbapenem-resistant gram-negative rods, in particular, CRE isolates.

9. Expert commentary

Aminoglycosides such as amikacin and gentamicin are established antibiotics that have been used for decades as a therapeutic option against many bacterial infections. The use of these agents in monotherapy has been discouraged due to their lower efficacy when compared to other antibiotics such as β-lactams [8,9] or due to the potential for aminoglycoside-related toxicity. However, aminoglycosides have been an important component of combination regimens in patients and are often used worldwide. Considering their role in the therapeutic armamentarium, primarily as part of combination regimens against severe gram-negative infections, some issues related to the clinical use of these agents may have been insufficiently studied. This includes evaluating the applicability of the current breakpoints to predict the effectiveness of aminoglycoside monotherapy.

Despite these gaps, with the emergence of polymyxin resistance in recent years, aminoglycosides have become a therapeutic option against CRE. This applies particularly to KPC-producing K. pneumoniae isolates with aminoglycosides used either in combination schemes or in monotherapy as the only remaining agent with in vitro activity. As reviewed here, the PK/PD target for aminoglycosides will very likely be achieved by monotherapy in critically ill patients, if the MIC of the infecting organism is slightly below or at the current breakpoints. This also applies to situations when doses higher than those usually prescribed are administered to critically ill patients. From this perspective, the CLSI breakpoints (e.g. 16 mg/L for amikacin and 4 mg/L for gentamicin) may be considered more problematic than the EUCAST breakpoints of 8 mg/L for amikacin and 2 mg/L for gentamicin. MIC-guided aminoglycoside dosing is a clinically feasible and promising scenario when treating critically ill patients with severe infections by CRE isolates, while the breakpoints have not yet been revisited.

The worldwide emergence of polymyxin-resistant CRE poses significant new challenges to antimicrobial therapy. Since aminoglycosides may be the single therapeutic option with in vitro activity against CRE isolates, the prescribing practices based on old aminoglycoside data need to be reassessed. Recent PK studies in critically ill patients have shown that individual dose adjustment is needed to ensure reasonable antimicrobial activity of aminoglycosides. Based on these recent PK studies with aminoglycosides in critically ill patients, the authors believe that aminoglycosides are unreliable as backbone agents if infecting CRE isolates present MICs at or slightly below the CLSI breakpoints. Indeed, the ‘susceptible’ label may hide some isolates that, in fact, will unlikely result in therapeutic success.

For these isolates with high MICs (i.e. an MIC of 16 mg/L for amikacin and 4 mg/L for gentamicin), doses up to 30–40 mg/kg of amikacin and 8–10 mg/kg of gentamicin may be necessary to achieve peak concentrations in plasma that approach the PK/PD target. Alternatively, the EUCAST breakpoints would provide ‘safer’ susceptibility predictions from a clinical perspective. However, based on the breakpoint of 8 mg/L for amikacin, the PK/PD target will be hardly attained even with high doses. On the other hand, PK studies show that the PK/PD target is more likely attained against gentamicin-susceptible CRE isolates with the MIC at the EUCAST breakpoint of 2 mg/L if high gentamicin doses are administered to critically ill patients.
10. Five-year view

New antimicrobial agents that offer activity against CRE, such as ceftazidime-avibactam and plazomicin among others, are in the pipeline or have been recently launched. However, these new drugs will not be available soon for many physicians worldwide, especially in low-income countries. Additionally, despite their in vitro activity, the role of some of these new drugs against CRE infections in critically ill patients, particularly in monotherapy, remains to be determined [56]. Thus, the authors believe that established aminoglycosides, such as amikacin and gentamicin, may be clinically beneficial and will be increasingly used against CRE isolates. While aminoglycoside monotherapy has been used in some patients against polymyxin-resistant CRE, rationally optimized aminoglycoside-based combination therapies hold significantly more promise against KPC-producing *K. pneumoniae*.

We anticipate that PK and PK/PD issues for aminoglycosides and their combination therapies as well as the PK/PD breakpoints in *Enterobacteriaceae* will be increasingly discussed in specialized journals. In this regard, the National Antimicrobial Susceptibility Testing Committee for the United States (USCAST) has recently released a document for public consultation addressing the issue of aminoglycosides breakpoints [57]. This will likely be extensively discussed and may lead to an adjustment of CLSI and EUCAST breakpoints of aminoglycosides for *Enterobacteriaceae*.

Finally, it is of paramount importance to assess the efficacy of aminoglycosides against CRE infections via future randomized controlled trials and/or prospective observational studies which account for PK/PD considerations in the clinical study design.

Key issues

- Aminoglycosides have been used as a therapeutic option against Gram-negative bacteria for several decades, even though they have been usually prescribed as a second agent in combination schemes in severe infections.
- The emergence of carbapenem-resistant *Enterobacteriaceae*, notably KPC-producing *Klebsiella pneumoniae* isolates, has highlighted the potential benefit of aminoglycosides, since many isolates remain susceptible to either amikacin or gentamicin. These antibiotics have been one of the very few or the only option in some KPC-producing *K. pneumoniae* with resistance to polymyxins.
- Some aminoglycoside-susceptible CRE isolates present minimal inhibitory concentration near or at the breakpoint: 16 mg/L (CLSI) and 8 mg/L (EUCAST) for amikacin; and 4 mg/L (CLSI) and 2 mg/L (EUCAST) for gentamicin.
- Recent pharmacokinetic studies in critically ill patients have shown that even with doses much higher than those usually prescribed, the PK/PD target for aminoglycosides will very unlikely be attained against isolates with these high minimal inhibitory concentrations. This may severely impair the antimicrobial activity in monotherapy.
- Aminoglycosides even at high doses in monotherapy are not reliable options for severe infections by high-MIC aminoglycoside-susceptible CRE isolates in critically ill patients. MIC-guided high dosage regimes and combination schemes are preferred for these infections.
- Although new antibiotics are in the pipeline or have been recently launched, we expect aminoglycosides to be increasingly prescribed against CRE isolates. The current breakpoints for aminoglycosides should be revised for CRE infections in critically ill patients.

Funding

This paper was not funded.

Declaration of interest

A.P. Zavascki has received honoraria for speaking engagements and consultancy from Merck, AstraZeneca, Pfizer and United Pharmaceuticals. J.B. Bulitta has received research support (not related to the content of this review) from Pfizer, Cubist, Trius, Cempra, Novartis, and Johnson & Johnson. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.


**Excellent review on the pharmacokinetics and pharmacodynamics of aminoglycosides.**

18. CLSI. Performance standards for antimirosurceptibility testing. PA, USA: Document M100-S26 Wayne; 2016.


**This study demonstrated synergy for aminoglycoside plus carbapenem combinations against P. aeruginosa isolates that were highly resistant to both antibiotics. Synergy could be exploited at clinically relevant antibiotic concentrations as shown via mechanism-based Monte Carlo simulations in the presence of the large between-patient variability in pharmacokinetics in critically ill patients.**


**Pharmacokinetic study in critically ill patients receiving high doses of either amikacin (30 mg/kg) or gentamicin (8 mg/kg) demonstrating that the target was achieved only in 59% of patients.**


**Pharmacokinetic study in critically ill patients in that a high fixed-dosing approach rather than a weight-based regimen is proposed.**


43. Van Duin D, Cober E, Richter SS, et al. Impact of therapy and strain type on outcomes in urinary tract infections caused by


- This study showed that inhibition of protein synthesis by an aminoglycoside resulted in decreased β-lactamase expression in *Pseudomonas aeruginosa*. This mechanism of synergy contributed to the suppression of emergence of bacterial resistance for aminoglycoside plus cefepime combination regimens.


- This study showed synergy of the amikacin plus doripenem combination against two CRE isolates that were resistant to both amikacin and doripenem. Synergy was shown in vitro and in a high-inoculum pneumonia infection model in neutropenic mice.


