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SYSTEMATIC REVIEW

What Antibiotic Exposures Are Required to Suppress the Emergence of Resistance for Gram-Negative Bacteria? A Systematic Review

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Abstract

Background The rates of antibiotic resistance in Gram-negative bacteria are increasing. One method to minimize resistance emergence may be optimization of antibiotic dosing regimens to achieve drug exposure that suppress the emergence of resistance.

Objective The aim of this systematic review was to describe the antibiotic exposures associated with suppression of the emergence of resistance for Gram-negative bacteria.

Methods We conducted a search of four electronic databases. Articles were included if the antibiotic exposure required to suppress the emergence of resistance in a Gram-negative bacterial isolate was described. Among studies, 57 preclinical studies (in vitro and in vivo) and 2 clinical studies 59 included investigated the monotherapy of antibiotics against susceptible and/or intermediate Gram-negative bacteria.

Results The pharmacokinetic/pharmacodynamic (PK/PD) indices reported to suppress the emergence of antibiotic resistance for various classes were β-lactam antibiotic minimum concentration to minimum inhibitory concentration (C_{min}/MIC) ≥ 4; aminoglycoside maximum concentration to MIC (C_{max}/MIC) ratio ≥ 20; fluoroquinolones, area under the concentration-time curve from 0 to 24 h to mutant prevention concentration (AUC_{24}/MPC) ≥ 35; tetracyclines, AUC_{24} to MIC (AUC_{24}/MIC) ratio ≥ 50; polymyxin B, AUC_{24}/MIC ≥ 808; and fosfomycin, AUC_{24}/MIC ≥ 3136. However, the exposures required to suppress the emergence of resistance varied depending on the specific antibiotic tested, the duration of the experiment, the bacterial species and the specific bacterial isolate tested. Importantly, antibiotic exposures required to suppress the emergence of resistance generally exceeded that associated with clinical efficacy.

Conclusion The benefits of implementing such high PK/PD targets must be balanced with the potential risks of antibiotic-associated toxicity.

Key Points

Generally, the antibiotic exposure for suppressing resistance emergence is higher than that associated with clinical efficacy.

The exposure required to suppress resistance emergence varies with bacterial species and specific isolates.

Resistance emergence may be more likely in the presence of a higher bacterial burden.

1 Introduction

The widespread use and misuse of antibiotics have led to the rapid emergence and global dissemination of antibiotic resistance [1, 2]. Currently, up to 70% of Gram-negative

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bacteria may harbor extended-spectrum β-lactamase (ESBL) enzymes depending on geographical location, conferring resistance to commonly used antibiotics such as piperacillin/tazobactam [3–5]. Commonly encountered multidrug-resistant bacteria may include carbapenem-resistant *Acinetobacter baumannii*, metallo-β-lactamase-producing *Pseudomonas aeruginosa*, and ESBL-producing *Klebsiella pneumoniae*, which are associated with increased morbidity and mortality in patients with a bacteraemia (odds ratio [OR] 2.98, 95% confidence interval [CI] 2.36–3.75; $p < 0.001$) [6].

Few new antibiotics and antibiotic combinations have been developed for the treatment of infections caused by resistant Gram-negative bacteria, such as plazomicin, ceftolozane/tazobactam, ceftazidime/avibactam, and meropenem/vaborbactam, however, resistance to these agents has been previously described [7, 8]. Therefore, given the cost and time required for the development of new antibiotics, methods to minimize resistance emergence to both new and old antibiotics are of paramount importance [9, 10]. One potential method is antibiotic dose optimization.

In vitro studies simulating current antibiotic dosing practices highlight that exposures associated with an increased probability of clinical cure may be insufficient to suppress the emergence of antibiotic-resistant Gram-negative bacteria [11, 12]. Pharmacokinetic/pharmacodynamic (PK/PD) indices relate the antibiotic exposure to the antibiotic susceptibility of an infecting pathogen where susceptibility may be described as the minimum inhibitory concentration (MIC), thereby providing the clinician with a dosing target. In studies investigating the PK/PD targets required for clinical efficacy, common indices include the percentage of the dosing interval that the drug concentration exceeds the pathogen MIC ($\%T_{>MIC}$, e.g. β-lactam antibiotics), the maximum drug concentration to MIC ratio (C_{max}/MIC, e.g. aminoglycosides) and the area under the drug concentration versus time curve (reflecting total antibiotic exposure) to MIC ratio (AUC/MIC, e.g. fluoroquinolones). Given that the MIC is a measure of susceptibility for the majority of the bacterial population at a standardized inoculum (5.5×10^5 colony-forming units per millilitre; CFU/mL), some studies have suggested that alternative measures of susceptibility reflecting the potential for resistance to develop may provide an advantage when determining the PK/PD targets required for suppressing resistance emergence. However, the inaccuracies in any MIC obtained by a single MIC test should also be considered due to assay variability [13]. One example is the mutant prevention concentration (MPC), which describes the antibiotic concentration required to suppress the growth of first-generation mutant bacteria that may selectively proliferate at concentrations above the MIC [14, 15]. The antibiotic concentration range between the MIC and the MPC is the mutant selection window (MSW). Antibiotic concentrations within the MSW promote the growth of resistant bacterial pathogens; thus, the antibiotic exposure required to suppress the emergence of resistance should be maintained above the MSW. Moreover, compared with MIC testing, MPC and MSW testing is conducted at higher bacterial burdens $> 1 \times 10^8$ CFU/mL, representing a serious bacterial infection that is more likely to facilitate resistance emergence than may be the case in common infection types [13, 16]. Overall, no standardized definitions exist to determine the antibiotic exposures that should be targeted to suppress the emergence of antibiotic resistance against different bacterial burdens. Moreover, there remains a lack of research to define target antibiotic exposures needed to minimize the development of resistance. Thus, this systematic review aims to describe the currently known antibiotic PK/PD indices required to suppress the emergence of Gram-negative bacterial antibiotic resistance.

2 Methods

A systematic review of the literature was performed according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [17].

2.1 Search Strategy

Four electronic databases (PubMed, EMBASE, SCOPUS, and Web of Science) were searched for studies, published between January 1953 and March 2019, investigating antibiotic exposures required to suppress the emergence of antibiotic resistance in Gram-negative bacteria. We designed the search strategy based on four concept areas as follows:

1. 'Anti-bacterial agents' (MeSH) OR 'anti-infective agents' (MeSH)) OR 'beta-lactams' (MeSH) OR 'penicillins' (MeSH) OR antibacter* OR anti-bacter* OR antimicrobial* OR anti-microbial OR antibiotic* OR anti-biotic* OR beta-lactam* OR penicillin* OR ampicillin OR piperacillin* OR cephalosporin* OR carbapenem* OR imipenem OR meropenem OR doripenem OR ertapenem OR cefepime OR polymyxin* OR colistin OR colisti* OR tobramicin OR tobramycin OR aminoglycoside* OR ceftaroline OR ciprofloxacin OR fosfomycin OR phosphonomycin* OR amikacin OR aztreonam OR gentamicin OR gentamycin OR levofloxacin OR ceftozolane OR moxifloxacin OR tigecycline OR minocycline OR glycylglycine OR tetracycline OR chloramphenicol OR rifampicin OR kanamycin.
2. Resistance OR multi-drug resistance OR drug resistance OR antibiotic resistance OR antimicrobial resistance.

3. Dose OR concentration OR exposure OR pharmacokinetic*.
4. Mutant prevention concentration OR mutant selection window OR suppress OR suppression OR pharmacodynamic*.

Each search was limited to English-language articles only. Finally, the searches (1), (2), (3) and (4) were combined with 'AND' as a Boolean Operator. In addition, the reference lists of included studies were searched manually to identify additional records.

2.2 Inclusion and Exclusion Criteria

Exposure for suppression of antibiotic resistance emergence was defined as an exposure that prevents the growth of the test bacteria on antibiotic-containing agar, or an increase in the MIC of the culture. This includes the complete eradication of the bacterial culture within the defined time frame of the experiment.

Inclusion criteria were as follows:

(a) *Antibiotic:* Currently clinically used for the treatment of infections in humans.
(b) *Microorganism:* Gram-negative bacteria.
(c) *Type of therapy and duration of exposure:* Monotherapy over any duration of exposure.
(d) *Study model:* In vitro pharmacodynamic model simulating human pharmacokinetics and/or in vivo animal model, or clinical study.
(e) *Outcome:* Antibiotic exposure and/or the PK/PD ratio required for the emergence of resistance suppression against previously susceptible and/or intermediate (according to the European Committee on Antimicrobial Susceptibility Testing [EUCAST] or Clinical and Laboratory Standards Institute [CLSI] definitions) Gram-negative bacteria.

Exclusion criteria were as follows:

(a) Review articles (systematic and narrative) and meta-analyses.
(b) Studies describing the pharmacodynamics of combination therapy with two or more antibiotics.
(c) Studies describing the emergence of antibiotic resistance in an in vivo microbiota that was distinct from the original experimental infection site.

2.3 Selection of Studies and Data Extraction

The reference management software EndNote X8 (Clarivate Analytics, Philadelphia, PA, USA) was used to manage all data retrieved from the four electronic databases. Two reviewers (CDS and AJH) independently screened all studies by title and abstract for full-text review. Both reviewers resolved any disagreement through consensus, or, if necessary, in consultation with a third reviewer (FBS). Relevant characteristics extracted from the full-text studies were study type (in vitro, in vivo, clinical study), antibiotic tested, bacterial isolate, experimental apparatus, simulated human pharmacokinetic profile (clearance [CL], drug exposures and/or dosing regimens, and elimination half-life [$t_{½}$]), baseline bacterial burden, method(s) for determination of the resistant subpopulation, and study outcomes in terms of the required drug exposures and PK/PD indices for suppression of emergence of resistance. Details of the protocol for this systematic review were registered on PROSPERO (ID: CRD42018098631).

2.4 Quality Assessment

Both reviewers independently assessed the methodological quality of the included studies and assessed their appropriateness for inclusion in this review. A list of methodological items was developed for quality assessment of the included preclinical (in vitro and in vivo) studies, described in a previous study [18] (Table 1). This list included a total of 11 items to assess a study's methodological quality, such as the aim of study, microorganism characterization, antibacterial agents, bacterial concentration, pharmacokinetic data, type of pharmacodynamic model used for the study, study observation period, control group, antibiotic concentration determination assay, resistant subpopulation selection, and outcomes. Moreover, there were a total of 17 sub-items and each sub-item was reported as 0 (not described) or 1 (described).

2.5 Outcomes and Data Analysis

The included studies were grouped into two categories based on study type: preclinical (in vitro and in vivo) or clinical studies. The outcomes of interest were used to identify the drug exposures and/or the PK/PD indices required to suppress the emergence of resistance. Suppression of emergence of resistance was defined as the presence of a bacterial population without an MIC shift and/or a bacterial burden below the lower limit of quantification (LLQ) on antibiotic-impregnated agar plates at any concentration over the duration of the experiment.

3 Results

Our search strategy identified 10,311 studies, of which 215 were selected for full-text review. Of those 215 studies, 156 were excluded, resulting in 59 studies being included in our

Table 1 Methodological items for quality assessment of the preclinical (in vitro and in vivo) studies

Items	Sub-items	Score[a]
Aim of the study	i. The question addressed in the study is clearly stated	0 or 1
Microorganism characterization	ii. Name of strain(s)	0 or 1
	iii. Type of strain(s), e.g. wild-type, clinical isolate, laboratory isolate(s)	0 or 1
	iv. Number of test strains	0 or 1
	v. Baseline MIC of the strain	0 or 1
Antibacterial agents	vi. Name of test antibacterial agent(s)	0 or 1
Bacterial concentration	vii. Baseline bacterial concentration used	0 or 1
Pharmacokinetic data	viii. Elimination half-life ($t_{½}$)	0 or 1
	ix. Drug exposure and/or dosing regimen	0 or 1
	x. Mode of administration	0 or 1
Type of pharmacodynamic model used for the study	xi. One-/two-compartment model (in vitro studies) or animal model (in vivo studies)	0 or 1
Study observation period	xii. Duration of study observation	0 or 1
Control group	xiii. Control group(s) without any antibiotic treatment used	0 or 1
Antibiotic concentration determination assay	xiv. Drug concentration measurement method	0 or 1
Resistant subpopulation selection	xv. Method(s) for resistant subpopulation selection: Resistant subpopulation may be identified by drug-supplemented media plates (with concentration drug specified) AND/OR at least one MIC performed per guidelines following antibiotic exposure	0 or 1
Outcomes	xvi. Drug exposure(s) for suppression of emergence of resistant	0 or 1
	xvii. Analysis of PK/PD indices for suppression of emergence of resistance: e.g. AUC/MIC, C_{max}/MIC, $T_{>MIC}$, or any new PK/PD indices described by the study for suppression of emergence of resistance	0 or 1

AUC area under the concentration-time curve, C_{max} maximum concentration, *MIC* minimum inhibitory concentration, *PK/PD*, pharmacokinetic/pharmacodynamic, *AUC/MIC* ratio of AUC and MIC, C_{max}/MIC ratio of C_{max} and MIC, $T_{>MIC}$ concentration of antibiotic times above the MIC

[a]The sub-items are scored as follows: 0, not reported; or 1, reported

systematic review. The complete search strategy and study selection process are presented in Fig. 1.

3.1 Study Characteristics

A summary description of the study characteristics and outcome measurements of the included preclinical in vitro 10659 studies is reported in Table 2. The 46 in vitro studies reported on exposures of β-lactams, carbapenems, fluoroquinolones, aminoglycosides, polymyxins, fosfomycin, tetracycline and glycylcyclines for suppression of emergence of resistance. Most in vitro studies ($n = 30$) used a two-compartment pharmacodynamic model as opposed to a one-compartment pharmacodynamic model ($n = 15$) to assess the antibiotic exposures against test Gram-negative bacteria. Only Alou et al. [31] used a multiple-compartment bladder infection model for their study. With the exception of that study, all studies had a study duration of at least 24 h. In Table 3, a summary of characteristics of the 11 included preclinical in vivo studies is presented. Most of the in vivo studies ($n = 6$) reported on β-lactam exposures for suppression of emergence of resistance. All in vivo studies were observed for at least for 24 h. Finally, the characteristics of the included clinical studies are summarized in Table 4. These clinical studies reported PK/PD indices for resistance suppression [76, 77]; however, the bacterial concentration at the site of infection was not determined in those studies.

3.2 Quality of Studies

As shown in electronic supplementary Table S1, among the preclinical in vitro studies, the quality assessment score range was 14–17, mode 16. Among 46 in vitro studies, 9 reported all the methodological quality assessment items. The studies that scored more than 14 provided information regarding the simulated pharmacokinetic profile. In the case of 11 preclinical in vivo studies, the range of quality assessment scores was 14–16, mode 15 (electronic supplementary Table S2). The total quality score data followed a skewed distribution, and the number of studies was not comparable between the in vitro and in vivo study groups. Quality assessment was not performed for the two clinical studies available for this review.

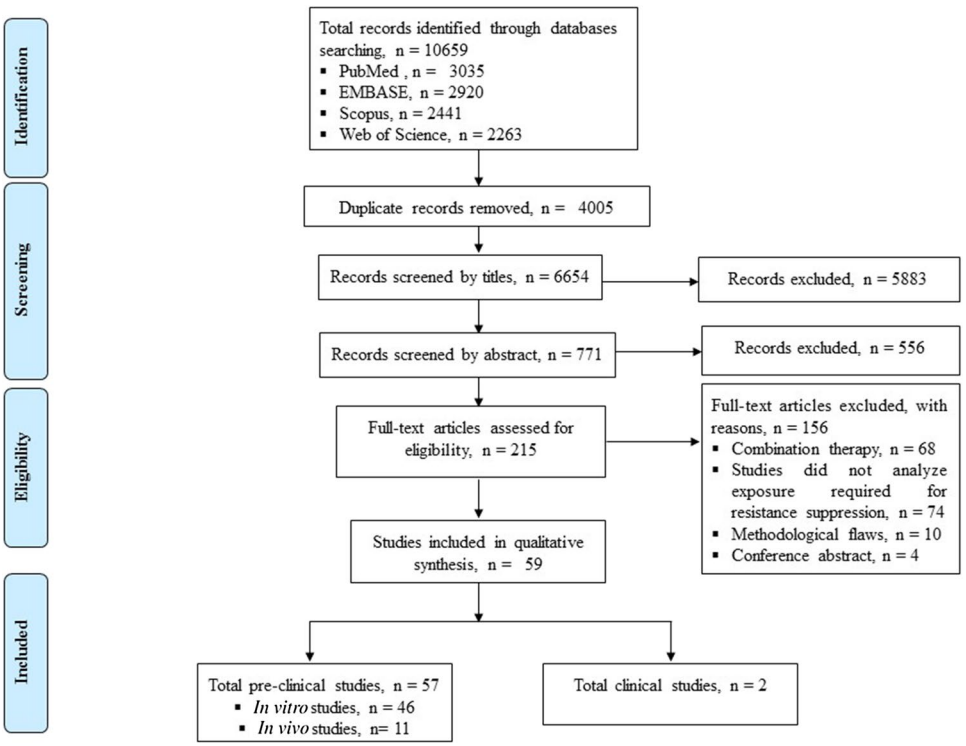

Fig. 1 Systematic literature search and selection process in accordance with the PRISMA guidelines. *PRISMA* Preferred Reporting Items for Systematic Reviews and Meta-Analyses

3.3 Study Outcomes

3.3.1 β-Lactams

As shown in Table 5, total and unbound $T_{>MIC}$ was the relevant PK/PD index describing the suppression of emergence of β-lactam antibiotic resistance in most included studies. Studies that were conducted for up to 72 h using a bacterial burden of 1×10^6 CFU/mL demonstrated that 100% $T_{>MIC}$ was sufficient to suppress the emergence of bacterial resistance for penicillins and cephalosporins. No in vitro study involving carbapenems was conducted for < 120 h. Studies that observed the emergence of resistance for a duration > 120 h suggest that for all β-lactam antibiotics, higher exposure with a minimum concentration (C_{min})/MIC ratio ranging from 1 to ~ 8 may be required to suppress resistance. Importantly, studies with a duration > 120 h also used a higher bacterial burden of > 1×10^7 CFU/mL compared with studies conducted for < 120 h that used a bacterial burden of ~ 1×10^6 CFU/mL. Only the study of a dynamic hollow-fibre infection model (HFIM) conducted by Felton et al. [40] directly compared the PK/PD indices required to suppress the emergence of bacterial resistance over the same time period for a high (~ 8×10^8 CFU/mL) and low (1×10^6 CFU/mL) initial bacterial burden (*Pseudomonas aeruginosa*). The exposure required to suppress the emergence of resistance for piperacillin/tazobactam administered as a bolus was a C_{min}/MIC of 3.4, compared with 4.6 against the high bacterial burden. When a 3 h prolonged infusion of piperacillin/tazobactam was employed, the C_{min}/MIC required to suppress the emergence of resistance was 10.4 and 11.9 for the low and high bacterial inoculum, respectively. However, against the low inoculum, achieving a piperacillin/tazobactam exposure of a C_{min}/MIC of 3.4 or 10.4, for the bolus and prolonged infusion, respectively, reduced the bacterial burden to below the LLQ over the study duration. In contrast, there was no significant bacterial killing against the high *P. aeruginosa* inoculum over the study duration [40].

Only one study has combined data for different β-lactam antibiotics (ceftazidime, cefepime and meropenem) to determine the exposure required for the suppression of emergence resistance for two *K. pneumoniae* and two *P. aeruginosa* isolates [58]. Classification and regression-tree analysis showed a β-lactam antibiotic C_{min}/MIC ≥ 3.8 is required to suppress the emergence of resistance against most isolates tested. Further evidence of a difference in the exposure required to suppress the emergence of resistance between bacterial species is demonstrated in experiments with ceftolozane/tazobactam. The approximate human dosing regimen of ceftolozane/tazobactam required to suppress the emergence of resistance for three *Escherichia coli* isolates (CTX-M-15, MIC 0.25 mg/L; CMY-10, MIC 1 mg/L; and a wild-type isolate, MIC 0.25 mg/L) and two *P. aeruginosa* isolates (a wild-type, MIC 0.5 mg/L; and a MexA/MexB efflux pump overexpressing isolate; MIC 4 mg/L) was ≥ 1/0.5 g and ≥ 2/1 g administered every 8 h as a 1 h infusion, respectively [42, 45]. In addition to the bacterial species, inoculum and MIC, specific bacterial phenotypes may influence the threshold required to

Table 2 Study characteristics of the preclinical in vitro studies

Author (year published)	Test antibiotic(s)	Simulated human pharmacokinetic profile		Test bacteria	No. of isolates	Study observation duration (h)	Study model(s)	Baseline bacterial concentration (CFU/ml)	Resistance determination method		Analysis of the PK/PD index to suppress the emergence of resistance
		Drug dose or exposure	$t_{½}$ (h)						Drug-supplemented media plates (at any concentration)	MIC	
Blaser et al. (1987) [19]	Enoxacin	500 mg po q12 h; 1 g q24 h		*K. pneumonia* *E. coli* *P. aeruginosa*	1 1 2	28	Two-compartment model	10^6	Yes	Yes	Yes
	Netilmicin	Equivalent to 2.5 mg/kg administered over 1 h q24 h, CI; 1 h infusion q8 h									
Strayer et al. (1994) [20]	Piperacillin	3 g bolus q6 h	~ 1	*P. aeruginosa* *E. coli*	1 2	24	Two-compartment model	10^6	Yes	Yes	NA
	Piperacillin/tazobactam	3/0.375 g bolus q6 h, 4/0.5 g bolus q8 h									
Palmer et al. (1995) [21]	Cefepime	2 g q12 h	2	*E. aerogenes* *K. pneumoniae*	2 1	48	Two-compartment model	10^6	Yes	Yes	NA
	Cefotaxime	2 g q8 h	2								
	Ceftriaxone	2 g q24 h	8								
Garrison et al. (1996) [22]	Ceftazidime	C_{max} 70 mg/L q8 h	2	*K. pneumoniae* *S. maltophilia*	1 18	24	Two-compartment model	~ 10^7	Yes	Yes	ND
	Ciprofloxacin	C_{max} 2.5 mg/L q12 h	3								
	Gentamicin	C_{max} 7 mg/L q12 h	4								
	Ticarcillin/clavulanate	C_{max} 325.8 mg/L q6 h	1.5								
Lamp and Vickers (1998) [23]	Ampicillin/sulbactam	1.5 g and 3 g infusion over 0.5 h q6 h	1	*E. coli*	3	24	Two-compartment model	10^6	No	Yes	Yes
Cappelletty (1999) [24]	Ceftazidime	2 g q8 h	2	*P. aeruginosa*	2	48	Two-compartment model	10^6	Yes	No	Yes
	Cefepime	2 g q8 h and q12 h	2.3								
		3 g q12 h and q24 h	5								
Tessier et al. (1999) [25]	Cefepime	1 g q12 h bolus; 1 g bolus loading dose followed by 2 g CI		*P. aeruginosa*	2	48	Two-compartment model	10^6	No	Yes	Yes
Ross et al. (2001) [26]	Levofloxacin	AUC_{24}/MIC = 1–150	8	*B. thetaiotaomicron*	1	24	One-compartment model	10^6	No	Yes	Yes
Peterson et al. (2002) [27]	Levofloxacin	AUC_{24}/MIC = 40–400	8	*B. fragilis*	3	24	Two-compartment model	10^6	No	Yes	Yes

Table 2 (continued)

Author (year published)	Test antibiotic(s)	Simulated human pharmacokinetic profile		Test bacteria	No. of isolates	Study observation duration (h)	Study model(s)	Baseline bacterial concentration (CFU/ml)	Resistance determination method		Analysis of the PK/PD index to suppress the emergence of resistance
		Drug dose or exposure	$t_{½}$ (h)						Drug-supplemented media plates (at any concentration)	MIC	
Noel et al. (2005) [28]	Moxifloxacin	AUC_{24}/MIC = 9–216 q24 h	10	*B. fragilis*	1 1	48	One-compartment model	10^8	Yes	No	Yes
Tam et al. (2005) [29]	Meropenem	C_{min}/MIC = 10; C_{min}/MIC = 6; C_{min}/MIC = 2; C_{min}/MIC = 0.25		*P. aeruginosa*	2	120	Two-compartment model	10^8	Yes	Yes	Yes
Tam et al. (2005) [30]	Polymyxin B	2.5 mg/kg/day in divided doses administered q8 h, q12 h, q24 h; 20 mg/kg/day q12 h	6	*P. aeruginosa*	4	96	Two-compartment model	10^5	Yes	Yes	Yes
Alou et al. (2006) [31]	Amoxicillin/clavulanic acid	2 g/125 mg q12 h (urine)		*E. coli*	6	12	Two-compartment model	10^7	No	Yes	ND
	Norfloxacin	400 mg q12 h (urine)									
Olofsson et al. (2006) [32]	Ciprofloxacin	C_{max} of 2–1024 × MIC	4	*E. coli*	3	24	One-compartment model	10^6	Yes	No	Yes
Olofsson et al. (2007) [33]	Ciprofloxacin	100–750 mg q12 h	4	*E. coli*	3	24	One-compartment model	10^7	No	Yes	Yes
Tam et al. (2008) [34]	Gentamicin	C_{max}/MIC = 4, q8 h; C_{max}/MIC = 12, q24 h	2.5	*P. aeruginosa* *A. baumannii*	1 1	72	Two-compartment model	10^7	Yes	Yes	Yes
	Amikacin	C_{max}/MIC = 6, q8 h; C_{max}/MIC = 5 and 13, q12 h; C_{max}/MIC = 20, q24 h									
Singh et al. (2009) [35]	Moxifloxacin	30–400 mg q24 h	12	*E. coli*	3	120	Two-compartment model	10^8	Yes	Yes	Yes

Table 2 (continued)

Author (year published)	Test antibiotic(s)	Simulated human pharmacokinetic profile		Test bacteria	No. of isolates	Study observation duration (h)	Study model(s)	Baseline bacterial concentration (CFU/ml)	Resistance determination method		Analysis of the PK/PD index to suppress the emergence of resistance
		Drug dose or exposure	$t_{½}$ (h)						Drug-supplemented media plates (at any concentration)	MIC	
Louie et al. (2010) [36]	Doripenem	500 mg infusion over 1 h q8 h; 500 mg; 1 g infusion over 4 h q8 h		*P. aeruginosa*	3	240	Two-compartment model	10^8	Yes	Yes	Yes
	Imipenem	500 mg infusion over 0.5 h q6 h; 1 g infusion over 1 h q8 h									
Louie et al. (2011) [37]	Moxifloxacin	50–250 mg q24 h	12	*Y. pestis*	1	240	Two-compartment model	10^8	Yes	Yes	Yes
Firsov et al. (2012) [38]	Doripenem	AUC_{24}/MIC = 60–180; administered in divided doses as an intermittent 1 h infusion q8 h	1	*P. aeruginosa*	3	72	Two-compartment model	10^8	Yes	Yes	Yes
	Imipenem	AUC_{24}/MIC = 30–120 infusion over 1 h q8 h									
Louie et al. (2012) [39]	Ceftaroline/NXL104	600 mg q8 h + 8 mg/L q8 h, q12 h, q24 h, and CI	2.5	*K. pneumonia* *E. cloacae*	3 1	240	Two-compartment model	10^7	Yes	No	Yes
Felton et al. (2013) [40]	Piperacillin/tazobactam	3–17 g q8 h administered as a 0.5 h infusion or 4 h infusion		*P. aeruginosa*	1	120	Two-compartment model	10^5 and 10^8	Yes	Yes	Yes
Firsov et al. (2013) [41]	Ciprofloxacin	AUC_{24}/MIC = 9–2880 and 15–720	4	*E. coli*	4	72	One-compartment model	10^8	Yes	Yes	Yes
VanScoy et al. (2013) [42]	Ceftolozane/tazobactam	25/62.5 mg to 1500/750 mg 1 h q8 h		*E. coli*	1	120	Two-compartment model	10^8	Yes	Yes	Yes

Table 2 (continued)

Author (year published)	Test antibiotic(s)	Simulated human pharmacokinetic profile		Test bacteria	No. of isolates	Study observation duration (h)	Study model(s)	Baseline bacterial concentration (CFU/ml)	Resistance determination method		Analysis of the PK/PD index to suppress the emergence of resistance
		Drug dose or exposure	$t_{½}$ (h)						Drug-supplemented media plates (at any concentration)	MIC	
Hagihara et al. (2014) [43]	Polymyxin B	1 mg/kg bolus q12 h	3.2	*A. baumannii*	4	24	One-compartment model	10^6	Yes	No	Yes
	Tigecycline	100 and 200 mg q12 h									
Li et al. (2014) [44]	Meropenem	0.5, 1 and 2 g over 0.5 h or 3 h infusion q8 h	1	*A. baumannii*	2	168	Two-compartment model	10^8	Yes	Yes	Yes
VanScoy et al. (2014) [45]	Ceftolozane/tazobactam	62.5/31.25 mg to 2/1 g over 1 h q8 h	2.5	*P. aeruginosa*	2	240	Two-compartment model	10^8	Yes	Yes	Yes
Werth and Rybak (2014) [46]	Ceftaroline/avibactam	600/600 mg q8 h	2.66 (ceftaroline), 1.8 (avibactam)	*B. fragilis* *P. bivia*	2 1	168	One-compartment model	10^8	Yes	No	Yes
	Ertapenem	1 g q24 h	4								
Docobo-Pérez et al. (2015) [47]	Fosfomycin	4–12 g infusion over 1 h q8 h; 24 g continuous infusion q24 h	4	*E. coli*	3	96	Two-compartment model	10^6	Yes	Yes	Yes
VanScoy et al. (2015) [48]	Fosfomycin	2–32 g q6 h, q8 h and q12 h, or CI; 0.25–8 g q8 h	2	*E. coli*	3	24	One-compartment model	10^6	Yes	Yes	Yes
Bergen et al. (2016) [49]	Piperacillin/tazobactam	4 g over 0.5 h q4 h, q6 h and q8 h	0.8, 1.4, 5.3	*P. aeruginosa*	1	168	Two-compartment model	10^7	Yes	Yes	Yes
Strukova et al. (2016) [50]	Ciprofloxacin	AUC_{24}/MIC = 15–2880; 7.5–2880; 3.75–1440	4	*K. pneumoniae*	3	72	One-compartment model	10^8	Yes	Yes	Yes
Strukova et al. (2016) [51]	Ciprofloxacin	AUC_{24}/MIC = 3.75–1440; 7.5–720; 7.5–1440	4	*P. aeruginosa*	4	72	One-compartment model	10^8	Yes	Yes	Yes
VanScoy et al. (2016) [52]	Fosfomycin	1–12 g q8 h	2	*E. coli*	1	240	Two-compartment model	10^8	Yes	Yes	ND
Alfouzan et al. (2017) [53]	Minocycline	200 mg q12 h	12	*A. baumannii*	3	48	Two-compartment model	10^6	Yes	No	Yes

Table 2 (continued)

Author (year published)	Test antibiotic(s)	Simulated human pharmacokinetic profile		Test bacteria	No. of isolates	Study observation duration (h)	Study model(s)	Baseline bacterial concentration (CFU/ml)	Resistance determination method		Analysis of the PK/PD index to suppress the emergence of resistance
		Drug dose or exposure	$t_{½}$ (h)						Drug-supplemented media plates (at any concentration)	MIC	
Bergen et al. (2017) [54]	Meropenem	0.5–2 g with 0.5 h infusion q8 h	1.1	*P. aeruginosa*	1	240	Two-compartment model	~ $10^{7.5}$	Yes	Yes	Yes
		0.5–2 g with 0.5 h infusion q8 h, and 1 g 12-hourly	4								
Ghazi et al. (2017) [55]	Amikacin	400 mg q12 h nebulized		*A. baumannii*	9	24	One-compartment model	10^6	No	Yes	ND
Soon et al. (2017) [56]	Ceftolozane/tazobactam	1, 2, 1/0.5, 2/1 g q8 h	2.3 (ceftolozane), 1 (tazobactam)	*E. coli*	4	240	Two-compartment model	10^6	Yes	No	ND
Strukova et al. (2017) [57]	Ciprofloxacin	AUC_{24}/MIC = 9–2880	4	*E. coli* *K. pneumonia* *P. aeruginosa*	4 4 3	72	One-compartment model	10^8	Yes	Yes	Yes
		AUC_{24}/MIC = 7.5–2880									
		AUC_{24}/MIC = 3.75–1440									
Tam et al. (2017) [58]	Cefepime	2 g infusion over 0.5 h q8 h	1	*K. pneumoniae* *P. aeruginosa*	2 2	120	Two-compartment model	10^8	Yes	Yes	Yes
	Ceftazidime	0.5, 3 or 4 g over 0.5 h q8 h									
	Meropenem	1 or 2 g over 0.5 h q8 h									
Zhanel et al. (2017) [59]	Fosfomycin	3 g po q24 h	6	*E. coli*	12	24	One-compartment model	10^6	No	Yes	Yes
Abbott et al. (2018) [60]	Fosfomycin	3 g po q24 h	5.7	*E. coli* *K. pneumonia* *E. cloacae*	9 8 7	72	Multiple-compartment bladder infection model	10^7	Yes	No	Yes
Sabet et al. (2018) [61]	Meropenem/vaborbactam	1/1, 1/2 and 2/2 g infusion over 3 h q8 h	1	*K. pneumoniae* *E. cloacae* *E. coli*	13 3 1	32	Two-compartment model	10^8	No	Yes	Yes

Table 2 (continued)

Author (year published)	Test antibiotic(s)	Simulated human pharmacokinetic profile		Test bacteria	No. of isolates	Study observation duration (h)	Study model(s)	Baseline bacterial concentration (CFU/ml)	Resistance determination method		Analysis of the PK/PD index to suppress the emergence of resistance
		Drug dose or exposure	$t_{½}$ (h)						Drug-supplemented media plates (at any concentration)	MIC	
Noel et al. (2018) [62]	Ceftolozane/tazobactam	1/0.5 g and 2/1 g over a 1 h infusion q8 h	2.5 (ceftolozane), 1 (tazobactam)	*E. coli* *K. pneumoniae* *P. aeruginosa*	3 2 5	168	One-compartment model	10^6	Yes	Yes	ND
	Meropenem	2 g bolus q8 h	1								
Barber et al. (2018) [63]	Ceftazidime/avibactam	2/0.5 g bolus q8 h	2.7	*K. pneumoniae* *C. freundii* *K. oxytoca*	2 1 1	96	One-compartment model	10^6	Yes	Yes	ND
	Meropenem	2 g bolus q8 h	1								
	Polymyxin B	1.25 mg/kg bolus q12 h	6								
	Amikacin	C_{max} 70–80 mg/L bolus q24 h	2								
	Tigecycline	200 mg bolus followed by 100 mg q12 h	42								
Abodakpi et al. (2019) [64]	Piperacillin/tazobactam	4 g piperacillin and 0.5/1/1/5/2/4 g tazobactam over a 30 min infusion q8 h	1	*K. pneumoniae* *E. coli*	3 1	72	Two-compartment model	10^6	Yes	No	Yes

A. baumannii Acinetobacter baumannii, *B. fragilis* Bacteroides fragilis, *B. thetaiotaomicron* Bacteroides thetaiotaomicron, *C. freundii* Citrobacter freundii, *E. aerogenes* Enterobacter aerogenes, *E. cloacae* Enterobacter cloacae, *E. coli* Escherichia coli, *K. pneumonia* Klebsiella pneumonia, *K. oxytoca* Klebsiella oxytoca, *P. aeruginosa* Pseudomonas aeruginosa, *P. bivia* Prevotella bivia, *S. maltophilia* Stenotrophomonas maltophilia, *Y. pestis* Yersinia pestis, AUC_{24} area under the drug concentration-time curve in a 24-h interval, AUC_{24}/MIC ratio of AUC_{24} and MIC, *CFU/mL* colony-forming unit per millilitre, *CI* continuous infusion, C_{max}/MIC ratio of C_{max} and MIC, C_{min}/MIC ratio of minimum drug concentration and MIC, C_{max} maximum drug concentration, *MIC* minimum inhibitory concentration, *NA* not available, *ND* not determined, *PO* orally, *PK/PD* pharmacokinetic/pharmacodynamic, *qxh* every × hours, $t_{½}$ elimination half-life

Table 3 Study characteristics of the preclinical in vivo studies

Author (year published)	Test antibiotic(s)	Simulated human pharmacokinetic profile		Test bacterium(a)	No. of isolates	Study observation duration (h)	Study model(s)	Baseline bacterial concentration (CFU/mL)	Resistance determination method		Analysis of PK/PD index to suppress the emergence of resistance
		Drug dose or exposure	$t_{½}$ (h)						Drug-supplemented media plates (at any concentration)	MIC	
Bakker-Woudenberg et al. (2006) [66]	Ceftazidime	6.3–1600 mg/kg/day q6 h, q12 h, and q24 h	NA	*K. pneumoniae*	1	48	Rat lung infection model	10^6	Yes	No	Yes
Jumbe et al. (2003) [65]	Levofloxacin	90, 215, or 600 mg/kg/day	NA	*P. aeruginosa*	1	24	Mice thigh infection model	10^8	Yes	No	Yes
Maciá et al. (2006) [67]	Ciprofloxacin	80 mg/kg/day q6 h	NA	*P. aeruginosa*	2	72	Mice murine pneumonia model	10^6	Yes	No	Yes
	Tobramycin	40 mg/kg/day q6 h									
Ong et al. (2007) [68]	Meropenem	6.25–2400 mg/kg/day q3 h to q24 h	NA	*P. aeruginosa*	3	24	Mice neutropenic and renally impaired thigh infection model	10^5 and 10^7	Yes	No	Yes
	Cefepime	1–600 mg/kg/day q6 h to q24 h									
Stearne et al. (2007) [69]	Ceftizoxime	6–1536 mg/kg/day q2 h, q4 h, q6 h; 384–1536 mg/kg/day q8 h	NA	*B. fragilis* *E. cloacae*	1 1	24	Mice subcutaneous abscess model	10^{7a}	Yes	No	Yes
Crandon et al. (2012) [70]	Ceftazidime/avibactam	2/0.5 g over 2 h q8 h	NA	*P. aeruginosa*	27	24	Mice neutropenic and immunocompetent thigh infection model	10^6 and 10^8	Yes	No	Yes
Louie et al. (2013) [71]	Meropenem	30–600 mg/kg/day	NA	*P. aeruginosa*	1	24	Murine pneumonia model	10^7	Yes	No	Yes
	Tobramycin	50–400 mg/kg/day									
Soubirou et al. (2015) [73]	Temocillin	200 mg/kg q2 h, q4 h and q6 h	NA	*E. coli*	2	24	Mice pyelonephritis model	10^5	Yes	Yes	Yes
Ni et al. (2014) [72]	Levofloxacin	5–40 mg/kg/day q24 h	NA	*E. coli*	1	24	Rabbit tissue cage infection model	~ 10^8	Yes	Yes	Yes
Pan et al. (2017) [29]	Fosfomycin	30–1200 mg/kg/day q8 h	NA	*E. coli* *P. aeruginosa*	1 1	72	Rabbit tissue cage infection model	10^8	Yes	Yes	Yes

Table 3 (continued)

Author (year published)	Test antibiotic(s)	Simulated human pharmacokinetic profile		Test bacterium(a)	No. of isolates	Study observation duration (h)	Study model(s)	Baseline bacterial concentration (CFU/mL)	Resistance determination method		Analysis of PK/PD index to suppress the emergence of resistance
		Drug dose or exposure	$t_{½}$ (h)						Drug-supplemented media plates (at any concentration)	MIC	
Abdelraouf et al. (2018) [75]	Plazomicin	28 mg/kg q24 h (15 mg/kg as a 0.5 h infusion q24 h)	NA	*K. pneumoniae*	4	24	Immunocompetent murine septicaemia model	~ 10^5	Yes	No	Yes
				E. coli	1						
				C. freundii	1						
				K. oxytoca	1						
	Meropenem	10.5–18 mg/kg q8 h (2 g over 3 h q8 h)		*M. morganii*	1						
	Tigecycline	1.66 mg/kg q12 h (50 mg q12 h)									

B. fragilis Bacteroides fragilis, *C. freundii* Citrobacter freundii, *E. cloacae* Enterobacter cloacae, *E. coli* Escherichia coli, *K. pneumonia* Klebsiella pneumonia, *K. oxytoca* Klebsiella oxytoca, *M. morganii* Morganella morganii, *P. aeruginosa* Pseudomonas aeruginosa, *CFU/mL* colony-forming unit per millilitre, *MIC* minimum inhibitory concentration, *NA* not available, *PK/PD* pharmacokinetic/pharmacodynamic, *qxh* every × hours, $t_{½}$ elimination half-life

[a]Stearne et al. [69] injected 10^7 CFU bacteria

suppress the emergence of resistance. An in vitro study in a two-compartment pharmacodynamic model by Cappelletty [24] compared mucoid and non-mucoid *P. aeruginosa* (both MIC 8 mg/L). Against the non-mucoid isolate, a cefepime exposure of 85% $T_{>MIC}$ suppressed the emergence of resistance. In contrast, the same exposure could not suppress the emergence of resistance against the mucoidal isolate.

The results of the in vivo studies are similar to the results of the in vitro studies conducted over 24 h. Meropenem and imipenem exposures of 40% $T_{>MIC}$ were reported to suppress the emergence of antibiotic resistance against three susceptible *P. aeruginosa* isolates (meropenem MICs 0.125, 0.25 and 1 mg/L; imipenem MICs 1, 1 and 1 mg/L) in a neutropenic murine model over 24 h (Table 6) [68]. In contrast, the exposures required to suppress the emergence of resistance in vitro for meropenem in studies conducted over > 120 h were a C_{min}/MIC of between 2 and 6 [54, 58].

3.3.2 Aminoglycosides

The relevant PK/PD ratio describing the suppression of emergence of aminoglycoside resistance is the C_{max}/MIC ratio (Table 5). Achieving a netilmicin C_{max}/MIC ratio of ≥ 8 mg/L suppressed the emergence of resistance in vitro, in the dynamic HFIM against *E. coli* (MIC 1 mg/L), *K. pneumoniae* (MIC 0.125 mg/L) and *P. aeruginosa* (MIC ≤ 8 mg/L).

Using the dynamic in vitro HFIM model, Tam et al. [34] demonstrated that an amikacin C_{max}/MIC of 13 or a C_{max}/MIC of 20 was required to suppress the emergence of resistance when administered twice or once daily, respectively, against *A. baumannii* (MIC 2 mg/L) over 72 h. Similarly, Ghazi et al. [55] reported that a simulated exposure following 400 mg of nebulized amikacin administered twice daily in an in vitro dynamic one-compartment model prevented the regrowth of resistant subpopulation of a clinical isolate of *A. baumannii* (MIC 2 mg/L).

For gentamicin, a C_{max}/MIC ratio of 30 when administered twice daily was reported to suppress the resistance emergence of *P. aeruginosa* (MIC 2 mg/L); however, even a C_{max}/MIC ratio > 36 when administered as a single-daily dose was unable to suppress the emergence of resistance [34]. The PK/PD indices identified in vitro were similar to those found in a mouse lung infection model study by Maciá et al. [67], who demonstrated that a plasma tobramycin C_{max}/MIC ratio of 19 when administered four times daily prevented the emergence of resistance against a wild-type *P. aeruginosa* (MIC 1 mg/L) in a murine pneumonia infection model (Table 6). In a separate murine pneumonia model, Louie et al. [71] reported that an AUC_{24}/MIC ratio ≥ 110.6 in the epithelial lining fluid of the lungs was required to suppress the resistance emergence of wild-type *P. aeruginosa* (MIC 1 mg/L).

Table 4 Study characteristics of the clinical studies

Author (year published)	Test antibiotic(s)	Simulated human pharmacokinetic profile		Test bacteria	No. of isolates	Study observation Duration (days)	Study model(s)	Baseline bacterial concentration (CFU/mL)	Resistance determination method		Analysis of PK/PD index to suppress the emergence of resistance
		Drug dose or exposure	$t_{½}$ (h)						Drug-supplemented media plates (at any concentration)	MIC	
Thomas et al. (1999) [76]	Cefmenoxime	1–2 g q4 h or q6 h	NA	*E. coli* *K. pneumoniae* *P. mirabilis* *H. influenzae* *E. cloacae* *S. marcescens*	14 17 6 6 11 11	3–31	107/143 patients included from four clinical trials databases	ND	No	Yes	Yes
	Ceftazidime	1–2 g q8 h or q12 h									
	Ciprofloxacin	200–300 mg q12 h, 400 mg q8 h or q12 h									
Hyatt and Schentag (2000) [77]	Ciprofloxacin		NA	*P. aeruginosa*	ND		635 patients identified between January 1993 and December 1996, using a computerized database	ND	No	No	Yes

E. cloacae Enterobacter cloacae, *E. coli* Escherichia coli, *H. influenza* Haemophilus influenza, *K. pneumonia* Klebsiella pneumonia, *P. aeruginosa* Pseudomonas aeruginosa, *P. mirabilis* Proteus mirabilis, *S. marcescens* Serratia marcescens, *CFU/mL* colony-forming unit per millilitre, *MIC* minimum inhibitory concentration, *NA* not available, *ND* not determined, *PK/PD* pharmacokinetic/pharmacodynamic, *qxh* every × hours, $t_{½}$ elimination half-life

Table 5 Study outcomes of the preclinical in vitro studies

Test antibiotic(s)	Name of test bacteria	Bacterial strain	Baseline MIC, mg/L (method)	Susceptibility (guideline)	Outcome of the study to suppress the emergence of resistance			References
					Approximate drug dose to suppress emergence of resistance	PK/PD indices		
						Total drug concentration	Unbound drug concentration	
Piperacillin	*E. coli*	WT J53	4 (CLSI)[a]	Susceptible (CLSI)[a]	3 g q6 h	100% $T_{>MIC}$	ND	[20]
	P. aeruginosa	ATCC 27853	8 (CLSI)[a]	Susceptible (CLSI)[a]	3 g q6 h	83% $T_{>MIC}$	ND	[20]
Piperacillin/tazobactam[d]	*E. coli*	WT J53	2/4 (CLSI)[a]	Susceptible (CLSI)[a]	3/0.375 g q6 h	100% $T_{>MIC}$, tazobactam 50% $T_{>4\ mg/L}$	ND	[20]
	E. coli	Isogenic J53.2-TEM-3 (TEM-3 expressed)	2/4 (CLSI)[a]	Susceptible (CLSI)[a]				
	P. aeruginosa	ATCC 27853	8/4 (CLSI)[a]	Susceptible (CLSI)[a]				
	P. aeruginosa	WT PAO1	4/4 (CLSI)	Susceptible (CLSI)	9 g infusion over 0.5 h q8 h	ND	fC_{min}/MIC = 3.4	[40]
					9 and 17 g infusion over 4 h q8 h	ND	fC_{min}/MIC = 10.4	[40]
	P. aeruginosa	Clinical isolate 1280	4/4 (CLSI)	Susceptible (CLSI)	4 g over 0.5 h q4 h, q6 h and q8 h		fC_{min}/MIC ≥ 5	[49]
	K. pneumoniae	Clinical isolate (CTX-M-15-producing)	32/4 (CLSI)	Resistant (CLSI)	4/1.5 g over a 30 min infusion q8 h	ND	$\%fT_{>MIC}$ of tazobactam ≥ 55.1	[64]
	E. coli	Clinical isolate (SHV-12 producing)	4/4 (CLSI)	Susceptible (CLSI)	4/1 g over a 30 min infusion q8 h	ND	$\%fT_{>MIC}$ of tazobactam ≥ 60	[64]
Ampicillin/sulbactam[e]	*E. coli*	ATCC 25922	4/2 (CLSI)[a]	Susceptible (CLSI)[a]	3 g over 0.5 h q6 h	≥ 77% $T_{>MIC}$	ND	[23]
	E. coli	EC11	4/2 (CLSI)[a]	Susceptible (CLSI)[a]				
	E. coli	TIM2	12/6 (CLSI)[a]	Intermediate (CLSI)				
Amoxicillin/clavulanic acid[f]	*E. coli*	Clinical isolate MR110 and MR61	4/2 (CLSI)	Susceptible (CLSI)	2 g/125 mg sustained release q12 h	100% $T_{>MIC}$	ND	[31]
	E. coli	Clinical isolate FJ8	8/2 (CLSI)	Susceptible (CLSI)				
	E. coli	Clinical isolate FJ16	16/2 (CLSI)	Intermediate (CLSI)				
Ticarcillin/clavulanate	*K. pneumoniae*	WT	ND	NA	~3/0.1 g q6h[k] [129]	ND	ND	[22]
Ceftriaxone	*E. aerogenes*	WT 3893	0.25 (CLSI)[a]	Susceptible (CLSI)[a]	2 g q24 h	ND	ND	[21]
Cefotaxime	*E. aerogenes*	WT 3893	0.125 (CLSI)	Susceptible (CLSI)	2 g q8 h	ND	ND	[21]
Ceftolozane	*P. aeruginosa*	ATCC BAA-47 (PAO1)	0.5/4 (CLSI)	Susceptible (CLSI)	1 g infusion over 1 h q8 h	100% $T_{>MIC}$	ND	[45]
	E. coli	WT 2805	0.25 (EUCAST)	Susceptible (CLSI)[a]	1 g q8 h	ND	ND	[56]
	E coli	Isogenic 2842 (CMY-10 β-lactamase-producing)	8.0 (CLSI)	Susceptible (CLSI)				
Ceftolozane/tazobactam[g]	*P. aeruginosa*	ATCC BAA-47 (PAO1)	0.5/4 (CLSI)	Susceptible (CLSI)	2/1 g infusion over 1 h q8 h	80% $T_{>MIC}$	ND	[45]

Table 5 (continued)

Test antibiotic(s)	Name of test bacteria	Bacterial strain	Baseline MIC, mg/L (method)	Susceptibility (guideline)	Outcome of the study to suppress the emergence of resistance			References
					Approximate drug dose to suppress emergence of resistance	PK/PD indices		
						Total drug concentration	Unbound drug concentration	
	P. aeruginosa	Clinical isolate PAE 2638	4/4 (CLSI)	Susceptible (CLSI)	2/1 g infusion over 1 h q8 h	100% $T_{>MIC}$	ND	[45]
	E. coli	Isogenic KC355192 (CTX-M-15 expressed)	0.25/4 (CLSI)	Susceptible (CLSI)[a]	750/375 mg 1 h q8 h	ND	ND	[42]
	E. coli	WT 2805	0.25/4 (EUCAST)	Susceptible (CLSI)[a]	1/0.5 g q8 h	ND	ND	[56]
	E. coli	Isogenic 2890 (AmpC β-lactamase-producing)	1/4 (EUCAST)	Susceptible (CLSI)[a]				
	E. coli	Clinical isolate 44913	0.12/4 (EUCAST)	Susceptible (EUCAST)	1/0.5 g over 1 h q8 h	ND	ND	[62]
	E. coli	Clinical isolate 49439 (CTX-M-15)	0.25/4 (EUCAST)	Susceptible (EUCAST)				
	E. coli	Clinical isolate 47202 (CTX-M-15)	0.25/4 (EUCAST)	Susceptible (EUCAST)				
	P. aeruginosa	Clinical isolate 17286	0.38/4 (EUCAST)	Susceptible (EUCAST)				
	P. aeruginosa	Clinical isolate 38475	0.5/4 (EUCAST)	Susceptible (EUCAST)				
	P. aeruginosa	Clinical isolate 47237 (OprD mutation, AmpC overexpression)	2/4 (EUCAST)	Susceptible (EUCAST)				
	P. aeruginosa	Clinical isolate 55759 (AmpC overexpression)	4/4 (EUCAST)	Susceptible (EUCAST)				
	P. aeruginosa	Clinical isolate 55762 (AmpC overexpression)	4/4 (EUCAST)	Susceptible (EUCAST)				
	K. pneumoniae	Clinical isolate 4329 (bla_{KPC}-producing)	0.5 (Etest)	Susceptible (EUCAST)	2/0.5 g bolus q8 h	ND	ND	[63]
	K. pneumoniae	Clinical isolate 11R (bla_{KPC}-producing)	0.19 (Etest)	Susceptible (EUCAST)				
	C. freundii	Clinical isolate 4299 (bla_{KPC}-producing)	0.19 (Etest)					
	K. oxytoca	Clinical isolate 6R (bla_{KPC}-producing)	0.75 (Etest)	Susceptible (EUCAST)				

Table 5 (continued)

Test antibiotic(s)	Name of test bacteria	Bacterial strain	Baseline MIC, mg/L (method)	Susceptibility (guideline)	Outcome of the study to suppress the emergence of resistance			References
					Approximate drug dose to suppress emergence of resistance	PK/PD indices		
						Total drug concentration	Unbound drug concentration	
Ceftaroline/avibactam[h]	*B. fragilis*	ATCC 25285	0.125/4[b]	NA	600/600 mg q8 h	ND	ND	[46]
	B. fragilis	Clinical isolate	2.0/4[b]					
	P. bivia	Clinical isolate	0.5/4[b]					
Ceftaroline/NXL104[i]	*K. pneumoniae*	Clinical isolate 27-908 M	0.75/4 (CLSI)	NA	600 mg q8 h + 8 mg/L q8 h, and CI	ND	ND	[39]
	K. pneumoniae	Clinical isolate 24-1318A	0.12/4.0 (CLSI)	NA	600 mg q8 h + 4 mg/L q8 h and q12 h			
	E. cloacae	Clinical isolate 2-77C	0.75/4.0 (CLSI)	NA	600 mg q8 h + 8 mg/L q8 h			
Ceftazidime	*P. aeruginosa*	WT Pa1	1.0 (EUCAST)	Susceptible (CLSI)[a]	3 g infusion over 0.5 h q8 h	C_{min}/MIC ≥ 7.7	ND	[58]
	P. aeruginosa	Clinical isolate C34	1.0 (CLSI)[a]	Susceptible (CLSI)[a]	2 g q8 h	100% $T_{>MIC}$	ND	[24]
	K. pneumoniae	WT Kp1	0.5 (EUCAST)	Susceptible (EUCAST)	3 or 4 g infusion over 0.5 h q8 h	C_{min}/MIC ≥ 3.8	ND	[58]
	E. aerogenes	WT 3893	≤ 0.5 (CLSI)[a]	Susceptible (CLSI)[a]	2 g q8 h	ND	ND	[21]
Cefepime	*P. aeruginosa*	WT Pa1	0.5 (EUCAST)	Susceptible (EUCAST)	2 g infusion over 0.5 h q8 h	C_{min}/MIC ≥ 2	ND	[58]
	P. aeruginosa	Clinical isolate PSA5	2.0 (CLSI)[a]	Susceptible (CLSI)[a]	1 g bolus q12 h, or 2 g CI q24 h	100% $T_{>MIC}$	ND	[25]
	K. pneumoniae	WT Kp1	0.25 (EUCAST)	Susceptible (EUCAST)	2 g infusion over 0.5 h q8 h	C_{min}/MIC ≥ 3.8	ND	[58]
	K. pneumoniae	WT 2324	2.0 (CLSI)	Susceptible (EUCAST)	2 g q12 h	ND	ND	[21]
	E. aerogenes	WT 3893	≤ 0.006 (CLSI)[a]	Susceptible (CLSI)[a]				
	E. aerogenes	Isogenic 3978 (ceftazidime-resistant depressed mutant)	0.5 (CLSI)[a]	Susceptible (CLSI)[a]				
	P. aeruginosa	Clinical isolate C34	8.0 (CLSI)[a]	Susceptible (CLSI)[a]	2 g q12 h	≥ 85% $T_{>MIC}$	ND	[24]
Meropenem	*P. aeruginosa*	ATCC 27853	1.0 (CLSI)	Susceptible (CLSI)	ND	ND	fC_{min}/MIC = 6	[29]
	P. aeruginosa	Isogenic AmpC (depressed AmpC-producing)	1.0 (CLSI)	Susceptible (CLSI)				

Table 5 (continued)

Test antibiotic(s)	Name of test bacteria	Bacterial strain	Baseline MIC, mg/L (method)	Susceptibility (guideline)	Outcome of the study to suppress the emergence of resistance			References
					Approximate drug dose to suppress emergence of resistance	PK/PD indices		
						Total drug concentration	Unbound drug concentration	
	P. aeruginosa	Clinical isolate 1280	0.25 (CLSI)	Susceptible (CLSI)	2 g infusion over 0.5 h q8 h	ND	fC_{min}/MIC = 2; 82% $fT_{>5\times MIC}$	[54]
					0.5–2 g infusion over 0.5 h q8 h, and 1 g 12-hourly	ND	fC_{min}/MIC > 31.6	
	P. aeruginosa	Clinical isolate 17286	6 (EUCAST)	Susceptible (EUCAST)	2 g bolus q8 h	ND	ND	[62]
	P. aeruginosa	Clinical isolate 38475	0.5 (EUCAST)	Susceptible (EUCAST)				
	P. aeruginosa	Clinical isolate 47237 (OprD mutation, AmpC overexpression)	2 (EUCAST)	Susceptible (EUCAST)				
	P. aeruginosa	Clinical isolate 55759 (AmpC overexpression)	2 (EUCAST)	Susceptible (EUCAST)				
	P. aeruginosa	Clinical isolate 55762 (AmpC overexpression)	4 (EUCAST)	Susceptible (EUCAST)				
	E. coli	Clinical isolate 44913	0.015(EUCAST)	Susceptible (EUCAST)				
	E. coli	Clinical isolate 49439 (CTX-M-15)	0.03 (EUCAST)	Susceptible (EUCAST)				
	E. coli	Clinical isolate 47202 (CTX-M-15)	0.03 (EUCAST)	Susceptible (EUCAST)				
	K. pneumoniae	Clinical isolate 55914 (CTX-M-15)	0.12(EUCAST)	Susceptible (EUCAST)				
	K. pneumoniae	Clinical isolate 55917 (CTX-M-15)	0.06(EUCAST)	Susceptible (EUCAST)				
	K. pneumoniae	WT Kp1	0.06 (EUCAST)	Susceptible (CLSI)	2 g infusion over 0.5 h q8 h	C_{min}/MIC ≥ 3.8	ND	[58]

Table 5 (continued)

Test antibiotic(s)	Name of test bacteria	Bacterial strain	Baseline MIC, mg/L (method)	Susceptibility (guideline)	Outcome of the study to suppress the emergence of resistance			References
					Approximate drug dose to suppress emergence of resistance	PK/PD indices		
						Total drug concentration	Unbound drug concentration	
	A. baumannii	Clinical isolate CSRA91	0.5 (CLSI)	Susceptible (CLSI)	2 g infusion over 0.5 h or 3 h q8 h	≥ 20% $T_{>MPC}$; $T_{>MPC/TMSW} \geq 0.25$	ND	[44]
	A. baumannii	Clinical isolate CSRA24	2.0 (CLSI)	Susceptible (CLSI)				
Meropenem/ vaborbactam[j]	*E. coli*	Clinical isolate EC1007	≤ 0.06/8 (CLSI)	Susceptible (CLSI)	2/2 g over a 3 h infusion q8 h	ND	ND	[61]
	E. cloacae	Clinical isolate ECL1058	0.125/8 (CLSI)	Susceptible (CLSI)				
	E. cloacae	Clinical isolate ECL1061	0.125/8 (CLSI)	Susceptible (CLSI)				
	E. coli	Clinical isolate EC1007	≤ 0.06/8 (CLSI)	Susceptible (CLSI)				
	K. pneumoniae	Clinical isolate KP1004	≤ 0.06/8 (CLSI)	Susceptible (CLSI)	1/1 g over a 3 h infusion q8 h	50% $T_{>MIC}$	ND	
	K. pneumoniae	Clinical isolate KP1061	≤ 0.06/8 (CLSI)	Susceptible (CLSI)				
	K. pneumoniae	Clinical isolate KP1087	0.25/8 (CLSI)	Susceptible (CLSI)	1/2 g over a 3 h infusion q8 h	ND	ND	
	K. pneumoniae	Clinical isolate KP1074	0.5/8 (CLSI)	Susceptible (CLSI)				
	K. pneumoniae	Clinical isolate KP1099	1/8 (CLSI)	Susceptible (CLSI)				
	K. pneumoniae	Clinical isolate KP1094	4/8 (CLSI)	Susceptible (CLSI)	2/2 g over a 3 h infusion q8 h	ND	ND	
	K. pneumoniae	Clinical isolate KP1100	4/8 (CLSI)	Susceptible (CLSI)				
	K. pneumoniae	Clinical isolate KP1194	8/8 (CLSI)	Susceptible (CLSI)	2/2 g over a 3 h infusion q8 h	ND	ND	
	K. pneumoniae	Clinical isolate KP1223	8/8 (CLSI)	Susceptible (CLSI)				
Doripenem	*P. aeruginosa*	WT PAO1	1.0 (CLSI)	Susceptible (CLSI)	1 g q8 h 4 h	51% $T_{>6.2\times MIC}$	ND	[36]
	P. aeruginosa	Clinical isolate 8996	1.0[b]	NA	~ 1 g infusion over 1 h q8h[k] [130, 137]	AUC_{24}/MIC = 170	ND	[38]
	P. aeruginosa	Clinical isolate 8997	1.0[b]	NA				
	P. aeruginosa	Clinical isolate 14051	1.0[b]	NA				
Imipenem	*P. aeruginosa*	Clinical isolate 8996	2.0[b]	NA	~ 500 mg infusion over 1 h q8h[k] [131]	AUC_{24}/MIC = 140	ND	[38]
	P. aeruginosa	Clinical isolate 8997	2.0[b]	NA				
	P. aeruginosa	Clinical isolate 14051	1.0[b]	NA				

Table 5 (continued)

Test antibiotic(s)	Name of test bacteria	Bacterial strain	Baseline MIC, mg/L (method)	Susceptibility (guideline)	Outcome of the study to suppress the emergence of resistance			References
					Approximate drug dose to suppress emergence of resistance	PK/PD indices		
						Total drug concentration	Unbound drug concentration	
Ertapenem	*B. fragilis*	ATCC 25285	0.25[b]	NA	1 g q24 h	ND	$fT_{>MIC}$ = 87.4%	[46]
	B. fragilis	Clinical isolate	2.0[b]	NA	1 g q24 h	ND	$fT_{>MIC}$ = 41.1%	[46]
	P. bivia	Clinical isolate	0.25[b]	NA	1 g q24 h	ND	$fT_{>MIC}$ = 87.4%	[46]
Amikacin	*A. baumannii*	ATCC BAA 747	4.0 (CLSI)	Susceptible (CLSI)	~ 1.5 mg/kg q12 h[k] [132]	C_{max}/MIC = 13	ND	[34]
					~ 2 mg/kg q24h[k] [132]	C_{max}/MIC = 20	ND	
Amikacin (aerosol)	*A. baumannii*	Clinical isolate ACBN 25–49	2.0 (CLSI)	Susceptible (CLSI)	400 mg q12h	ND	ND	[55]
Gentamicin	*P. aeruginosa*	ATCC 27853	2.0 (CLSI)	Susceptible (CLSI)	3 mg/kg q12h[k] [133]	C_{max}/MIC = 30	ND	[34]
Netilmicin	*K. pneumoniae*	ATCC 13883	0.125[b]	NA	2.5 mg/kg infusion over 1 h q24 h	C_{max}/MIC ≥ 8	ND	[19]
	E. coli	ATCC 25922	1.0[b]	NA				
	P. aeruginosa	ATCC 27853	4.0[b]	NA				
	P. aeruginosa	Clinical isolate A-10	8.0[b]	NA				
Ciprofloxacin	*E. coli*	CCUG 17620	0.008 (CLSI)	Susceptible (CLSI)	< 400 mg q12 h[k] [134]	AUC_{24}/MPC ≥ 22	ND	[32]
	E. coli	Clinical isolate Nu14	0.008 (CLSI)	Susceptible (CLSI)	< 400 mg q12 h[k] [134]	AUC_{24}/MPC ≥ 22	ND	[32]
	E. coli	Isogenic Nu118 (a gyrA mutant)	0.047 (CLSI)	Susceptible (CLSI)	< 400 mg q12h[k] [134]	AUC/MPC = 11	ND	[32]
	E. coli	WT LM347	0.012 (Etest)	NA	< 400 mg q12h	AUC_{24}/MPC ≥ 14	ND	[33]
	E. coli	ATCC 25922	0.008 (CLSI)	Susceptible (CLSI)	≥ 400 mg q8h[k] [134]	AUC_{24}/MIC = 1080 ± 416 AUC_{24}/MPC = 58 ± 35	ND	[41, 57]
	E. coli	Clinical isolate 4300	0.016 (CLSI)	Susceptible (CLSI)				
	E. coli	Clinical isolate 4454	0.016 (CLSI)	Susceptible (CLSI)				
	E. coli	Isogenic GM2995 (carrying *MutD5* mutator) [135]	0.016 (CLSI)	Susceptible (CLSI)				
	K. pneumoniae	Clinical isolate 1885	1.0 (CLSI)	Susceptible (CLSI)	≥ 400 mg q8h[k] [134]	AUC_{24}/MIC = 300–1400 AUC_{24}/MPC ≥ 30	ND	[50, 57]
	K. pneumoniae	Clinical isolate 1145	0.5 (CLSI)	Susceptible (CLSI)				
	K. pneumoniae	Clinical isolate 185	0.125 (CLSI)	Susceptible (CLSI)				
	P. aeruginosa	Clinical isolates 45	0.5 (CLSI)	Susceptible (CLSI)	≥ 400 mg q8h[k] [134]	AUC_{24}/MIC = 300–1400 AUC_{24}/MPC ≥ 30	ND	[51, 57]
	P. aeruginosa	Clinical isolates 279	0.5 (CLSI)	Susceptible (CLSI)				
	P. aeruginosa	Clinical isolates 817	0.5 (CLSI)	Susceptible (CLSI)				
	P. aeruginosa	Clinical isolates 395	0.125 (CLSI)	Susceptible (CLSI)				

Table 5 (continued)

Test antibiotic(s)	Name of test bacteria	Bacterial strain	Baseline MIC, mg/L (method)	Susceptibility (guideline)	Outcome of the study to suppress the emergence of resistance			References
					Approximate drug dose to suppress emergence of resistance	PK/PD indices		
						Total drug concentration	Unbound drug concentration	
	K. pneumoniae	WT	NA	NA	200 mg bolus q12h[k] [134]	ND	ND	[22]
Enoxacin	*K. pneumoniae*	ATCC 13883	0.25[b]	NA	500 mg po q12h and q24 h	C_{max}/MIC = 20	ND	[19]
	E. coli	ATCC 25922	0.125[b]	NA		C_{max}/MIC ≥ 8	ND	
	P. aeruginosa	ATCC 27853	8.0[b]	NA		C_{max}/MIC ≥ 8	ND	
	P. aeruginosa	Clinical isolate A-10	1.0[b]	NA		C_{max}/MIC ≥ 8	ND	
Levofloxacin	*B. fragilis*	ATCC 25285	2 (CLSI)[a]	NA	~ 1.25 g q24 h[k] [136]	AUC_{24}/MIC = 62	ND	[27]
	B. fragilis	ATCC 23745	4 (CLSI)[a]	NA	~ 1.75 g q24 h[k] [136]	AUC_{24}/MIC = 44	ND	
	B. fragilis	Clinical isolate M97-117	2 (CLSI)[a]	NA	~ 2.75 g q24 h[k] [136]	AUC_{24}/MIC = 134	ND	
	B. thetaiotaomicron	ATCC 29741	8.0 (CLSI)[a]	NA	~ 6.25 g q24 h[k] [136]	AUC_{24}/MIC ≥ 75	ND	[26]
Moxifloxacin	*E. coli*	ATCC 25922	0.0625 (CLSI)	Susceptible (CLSI)	80 mg q24 h	AUC_{24}/MIC = 117	ND	[35]
	E. coli	WT MG1655	0.0625 (CLSI)	Susceptible (CLSI)	120 mg q24 h	AUC_{24}/MIC = 180	ND	[35]
	E. coli	WT EC28044	0.0625 (CLSI)	Susceptible (CLSI)	400 mg q24 h	AUC_{24}/MIC = 627	ND	[35]
	E. coli	WT LM347	0.032 (Etest)	NA	400 mg q24 h	AUC_{24}/MIC = 1098	ND	[33]
	E. coli	Isogenic LM378 (a gyrA single mutant)	0.25 (Etest)	NA				
	Y. pestis	Isogenic ΔCO92 (an avirulent mutant lacking pCD1 plasmid with low response simulation	0.06 (CLSI)	Susceptible (CLSI)	≥ 175 mg infusion over 1 h q24 h, or CI	ND	fC_{max}/MIC ≥ 16.8	[37]
	B. fragilis	WT SMH2612	1.0 (CLSI)	Susceptible (CLSI)	≥ 90 mg q12 h	AUC_{24}/MIC ≥ 9	ND	[28]
Norfloxacin	*E. coli*	Clinical isolate FJ16	≤ 0.25 (CLSI)	Susceptible (CLSI)	400 mg po q12 h	AUC_{12}/MIC ≥ 3092	ND	[31]
	E. coli	Clinical isolate FJ32	≤ 0.25 (CLSI)	Susceptible (CLSI)				
	E. coli	Clinical isolate FJ 64	≤ 0.25 (CLSI)	Susceptible (CLSI)				
	E. coli	WT LM347	0.064 (Etest)	NA	200 mg q12 h	AUC_{24}/MIC = 114		[33]
	E. coli	Isogenic LM421 (a gyrA/marR double mutant)	4.0 (Etest)	NA				
Fosfomycin[c]	*E. coli*	Clinical isolate Ec46	1.0 (CLSI)	Susceptible (CLSI)	24 g q24 h in divided doses, or CI	ND	$fAUC_{24}$/MIC ≥ 3136 h	[47]

Table 5 (continued)

Test antibiotic(s)	Name of test bacteria	Bacterial strain	Baseline MIC, mg/L (method)	Susceptibility (guideline)	Outcome of the study to suppress the emergence of resistance			References
					Approximate drug dose to suppress emergence of resistance	PK/PD indices		
						Total drug concentration	Unbound drug concentration	
	E. coli	ATCC 25922	1.0 (CLSI)	Susceptible (CLSI)	≥ 2 g q6 h	ND	32.8% $fT_{>RIC}$	[48]
	E. coli	Clinical isolate 2692	1.0 (CLSI)	Susceptible (CLSI)				
	E. coli	Clinical isolate 13319	1.0 (CLSI)	Susceptible (CLSI)				
	E. coli	ATCC 25922	2.0	Susceptible (CLSI)	4 g q8 h	ND	ND	[52]
	E. coli	Clinical isolate 41	0.5 (EUCAST)	Susceptible (EUCAST)	3 g po q24 h	ND	$fAUC_{24}$/MIC = 1805	[60]
	E. cloacae	Clinical isolate 94	1.0 (EUCAST)	Susceptible (EUCAST)				
	E. cloacae	Clinical isolate 21	8.0 (EUCAST)	Susceptible (EUCAST)				
	E. coli	Clinical isolate 11	0.5 (EUCAST)	Susceptible (EUCAST)				
	E. coli	Clinical isolate 39	0.5 (EUCAST)	Susceptible (EUCAST)				
	E. coli	Clinical isolate 35166	0.5 (EUCAST)	Susceptible (EUCAST)				
	E. coli	Clinical isolate 12620	2.0 (EUCAST)	Susceptible (EUCAST)				
	E. coli	Clinical isolate 1016	16.0 (EUCAST)	Susceptible (EUCAST)				
	E. coli	WT 79968	1.0 (CLSI)	Susceptible (CLSI)	3 g po q24 h	ND	$fAUC_{24}$/MIC ≥ 7250 100% $fT_{>MIC}$	[59]
	E. coli	Clinical isolate 89439	1.0 (CLSI)	Susceptible (CLSI)				
	E. coli	Clinical isolate ECMH01	1.0 (CLSI)	Susceptible (CLSI)				
	E. coli	Clinical isolate 80083	1.0 (CLSI)	Susceptible (CLSI)				
	E. coli	Clinical isolate 85332	1.0 (CLSI)	Susceptible (CLSI)				
	E. coli	Clinical isolate 88273	1.0 (CLSI)	Susceptible (CLSI)				
	E. coli	Clinical isolate 90087	1.0 (CLSI)	Susceptible (CLSI)				
	E. coli	Clinical isolate 90789	1.0 (CLSI)	Susceptible (CLSI)				
	E. coli	Clinical isolate 95882	1.0 (CLSI)	Susceptible (CLSI)				
	E. coli	Clinical isolate 80960	4.0 (CLSI)	Susceptible (CLSI)				
	E. coli	Clinical isolate 92969	4.0 (CLSI)	Susceptible (CLSI)				
	E. coli	Clinical isolate N-10-1631	4.0 (CLSI)	Susceptible (CLSI)				
Polymyxin B	*P. aeruginosa*	WT PA 27853	1.0 (Etest)	NA	20 mg/kg/day q12 h	ND	ND	[30]
	A. baumannii	Clinical isolate 31	1.0 (CLSI)	Susceptible (CLSI)	1 mg/kg q12 h	ND	$fAUC_{12}$/MIC ~ 80	[43]
	A. baumannii	Clinical isolate 32	1.0 (CLSI)	Susceptible (CLSI)				
	A. baumannii	Clinical isolate 33	1.0 (CLSI)	Susceptible (CLSI)				
	A. baumannii	Clinical isolate 35	1.0 (CLSI)	Susceptible (CLSI)				

Table 5 (continued)

Test antibiotic(s)	Name of test bacteria	Bacterial strain	Baseline MIC, mg/L (method)	Susceptibility (guideline)	Outcome of the study to suppress the emergence of resistance			References
					Approximate drug dose to suppress emergence of resistance	PK/PD indices		
						Total drug concentration	Unbound drug concentration	
Minocycline	*A. baumannii*	WT SMD 33980	0.5[b]	NA	400 mg/day	ND	$fAUC_{24}$/MIC = 20–25	[53]
	A. baumannii	Clinical isolate SMD 35406	3.0[b]	NA				
	A. baumannii	Clinical isolate SMD 34958	4.0[b]	NA				
Tigecycline	*A. baumannii*	Clinical isolate 31	1 (CLSI)	Susceptible (CLSI)	100 and 200 mg q12 h	ND	$fAUC_{12}$/MIC = 6.0 at 100 mg $fAUC_{12}$/MIC = 8.7 at 200 mg	[43]
	A. baumannii	Clinical isolate 32	1 (CLSI)	Susceptible (CLSI)				
	A. baumannii	Clinical isolate 33	1 (CLSI)	Susceptible (CLSI)	100 and 200 mg q12 h	ND	$fAUC_{12}$/MIC = 1.5 at 100 mg $fAUC_{12}$/MIC = 2.2 at 200 mg	
	A. baumannii	Clinical isolate 35	1 (CLSI)	Susceptible (CLSI)				

A. baumannii Acinetobacter baumannii, *B. fragilis* Bacteroides fragilis, *B. thetaiotaomicron* Bacteroides thetaiotaomicron, *C. freundii* Citrobacter freundii, *E. aerogenes* Enterobacter aerogenes, *E. cloacae* Enterobacter cloacae, *E. coli* Escherichia coli, *K. pneumonia* Klebsiella pneumonia, *K. oxytoca Klebsiella oxytoca, P. aeruginosa* Pseudomonas aeruginosa, *P. bivia* Prevotella bivia, *Y. pestis* Yersinia pestis, AUC_{24} area under the drug concentration-time curve in a 24-h interval, *ATCC* American Type Culture Collection, *CCUG* Culture Collection University of Gothenburg, *CI* continuous infusion, *CLcr* creatinine clearance, *CLSI* Clinical and Laboratory Standards Institute, C_{max} maximum concentration of antibiotic, $fAUC_{12}$ area under the free drug concentration-time curve in a 12-h interval, $fAUC_{24}$ area under the free-drug concentration-time curve in a 24-h interval fC_{min} minimum free drug concentration, *EUCAST* European Committee on Antimicrobial Susceptibility Testing, $fT_{>MIC}$, percentage of time of the dosing interval during which free-drug concentrations remained above the MIC for the corresponding strain, *MIC* minimum inhibitory concentration, *MPC* mutant prevention concentration, *NA* not available, *ND* not determined, *PK/PD* pharmacokinetic/pharmacodynamic, *po* orally, *qxh* every × hours, *RIC* resistance inhibitory concentration, *TMSW* time within the mutation selection window, *WT* wild type

[a]MIC was determined by the National Committee for Clinical Laboratory Standards (NCCLS), currently known as the CLSI

[b]MIC determination guideline (CLSI/EUCAST/Etest) was not mentioned in the study

[c]MIC of fosfomycin was determined by supplementation with 25 mg/L of glucose-6-phosphate (G6P) in medium

[d]MIC of piperacillin was determined in the presence of 4 mg/L of tazobactam [20, 40]

[e]MIC of ampicillin was determined in the presence of 2 and 6 mg/L of sulbactam [23]

[f]MIC of amoxicillin was determined in the presence of 2 mg/L of clavulanic acid [31]

[g]MIC of ceftolozane was determined in the presence of 4 mg/L of tazobactam [42, 45]

[h]MIC of ceftaroline was determined in the presence of 4 mg/L of avibactam [46]

[i]MIC of ceftaroline was determined in the presence of 4 mg/L of NXL104 [39]

[j]MIC of meropenem was determined in the presence of 8 mg/L of vaborbactam [61]

[k]Approximate dose of antibiotics was calculated considering CLcr ~ 100 and weight 80 kg [136]

Table 6 Study outcomes of preclinical in vivo studies

Test antibiotic(s)	Name of test bacteria	Bacterial strain	Baseline MIC, mg/L (method)	Susceptibility	Outcome of the study to suppress the emergence of resistance			References
					Approximate drug dose to suppress emergence of resistance	PK/PD indices		
						Total drug concentration	Unbound drug concentration	
Temocillin	*E. coli*	WT CFT073-RR	4.0(CLSI)	Susceptible (CLSI)	200 mg/kg q2 h, q4 h and q6 h	ND	41% $fT > MIC$ at q4 h	[73]
	E. coli	Isogenic CFT073-RR-CTX-M-15b	8.0(CLSI)	Susceptible (CLSI)	200 mg/kg q2 h, q4 h and q6 h	ND	23% $fT > MIC$ at q6 h	
Ceftazidime	*K. pneumoniae*	ATCC 43816	0.5 (CLSI)	Susceptible (CLSI)	1600 mg/kg/day q6 h, q12 h and q24 h	ND	24.5% $fT_{>MIC}$ at q6 h	[66]
Ceftazidime/avibactam[d]	*P. aeruginosa*	Clinical isolate 971	4/4 (CLSI)	Susceptible (CLSI)	2/0.5 g over 2 h q8 h	ND	87% $fT_{>MIC}$	[70]
	P. aeruginosa	Clinical isolate 22	4/4 (CLSI)	Susceptible (CLSI)				
	P. aeruginosa	Clinical isolate 3607	4/4 (CLSI)	Susceptible (CLSI)				
	P. aeruginosa	Clinical isolate 1383	4/4 (CLSI)	Susceptible (CLSI)				
	P. aeruginosa	Clinical isolate 1384	4/4 (CLSI)	Susceptible (CLSI)				
	P. aeruginosa	Clinical isolate AZ37-8	4/4 (CLSI)	Susceptible (CLSI)				
	P. aeruginosa	Clinical isolate 856	8/4 (CLSI)	Susceptible (CLSI)	2/0.5 g over 2 h q8 h	ND	87% $fT > MIC$	
	P. aeruginosa	Clinical isolate 1387	8/4 (CLSI)	Susceptible (CLSI)				
	P. aeruginosa	Clinical isolate 1389	8/4 (CLSI)	Susceptible (CLSI)				
	P. aeruginosa	Clinical isolate 1382	8/4 (CLSI)	Susceptible (CLSI)				
	P. aeruginosa	Clinical isolate 1386	8/4 (CLSI)	Susceptible (CLSI)				
	P. aeruginosa	Clinical isolate 1388	8/4 (CLSI)	Susceptible (CLSI)				
	P. aeruginosa	Clinical isolate AZ24-2	8/4 (CLSI)	Susceptible (CLSI)				
	P. aeruginosa	Clinical isolate AZ28-19	8/4 (CLSI)	Susceptible (CLSI)				
	P. aeruginosa	Clinical isolate JJ4-32	8/4 (CLSI)	Susceptible (CLSI)				
	P. aeruginosa	Clinical isolate JJ4-39	8/4 (CLSI)	Susceptible (CLSI)				
	P. aeruginosa	Clinical isolate JJ-69	8/4 (CLSI)	Susceptible (CLSI)				
	P. aeruginosa	Clinical isolate JJ8-16	8/4 (CLSI)	Susceptible (CLSI)				
Ceftizoxime	*B. fragilis*	ATCC 23745	1.0 (CLSI)[a]	Susceptible (CLSI)[a]	384–1536 mg/kg/day q2 h, q4 h, q6 h, q8 h	ND	ND	[69]
	E. cloacae	Clinical isolate 22491	0.25 (CLSI)[a]	Susceptible (CLSI)[a]	>384 mg/kg/day q2 h; 1536 mg/kg/day q4 h	ND	$fAUC_{24}/MIC > 1000$	

Table 6 (continued)

Test antibiotic(s)	Name of test bacteria	Bacterial strain	Baseline MIC, mg/L (method)	Susceptibility	Outcome of the study to suppress the emergence of resistance			References
					Approximate drug dose to suppress emergence of resistance	PK/PD indices		
						Total drug concentration	Unbound drug concentration	
Cefepime	*P. aeruginosa*	WT PAO1 (K767)	1.0 (CLSI)	Susceptible (CLSI)	ND	42% $T_{>MIC}$	> 100% $fT_{>MIC}$	[35]
	P. aeruginosa	Isogenic K767 + (overexpressing the MexA-MexB-OprM efflux systems)	8.0 (CLSI)	Susceptible (CLSI)	ND	61% $T_{>MIC}$	> 100% $fT_{>MIC}$	
Meropenem	*P. aeruginosa*	WT PAO1 (K767)	0.25 (CLSI)	Susceptible (CLSI)	ND	21% $T_{>MIC}$	40% $fT_{>MIC}$	[68]
	P. aeruginosa	Isogenic K767 + (overexpressing the MexA-MexB-OprM efflux systems)	0.125 (CLSI)	Susceptible (CLSI)	ND	36% $T_{>MIC}$	40% $fT_{>MIC}$	
	P. aeruginosa	Isogenic ΔK767 (MexA-MexB-OprM deleted pumps)	1.0 (CLSI)	Susceptible (CLSI)	ND	26% $T_{>MIC}$	40% $fT_{>MIC}$	
	K. pneumoniae	Isolate no. 557 [aadA2, bla_{TEM-1}, bla_{SHV-11}, aac(6′)-Ib, bla_{KPC-2}, aph(3′)-Ia]	8	Susceptible (CLSI)	2 g over 3 h q8 h	ND	$fT_{>MIC} \geq 75\%$	[75]
	K. pneumoniae	Isolate no. 558 [aac(3)-IId, aadA2, bla_{TEM-1}, aph(6)-Ia, bla_{SHV-11}, blaKPC-3, aph(6)-Id]	> 32	Resistant (CLSI)				
	K. pneumoniae	Isolate no. 559 [bla_{TEM-1}, bla_{SHV-11}, aac(3)-IIa, $bla_{CTX-M-15}$, aac(6′)-Ib-cr, bla_{OXA-48}, bla_{OXA-1}, bla_{OXA-30}]	> 32	Resistant (CLSI)				
	E. coli	Isolate no. 471 (aac(3)-IId, bla_{TEM-1}, EC-6 (intrinsic AmpC)	0.03	Susceptible (CLSI)				
	C. freundii	Isolate no. 38 [blaCMY-48-like (intrinsic gene), aac(6′)-If]	0.06	Susceptible (CLSI)				

Table 6 (continued)

Test antibiotic(s)	Name of test bacteria	Bacterial strain	Baseline MIC, mg/L (method)	Susceptibility	Outcome of the study to suppress the emergence of resistance			References
					Approximate drug dose to suppress emergence of resistance	PK/PD indices		
						Total drug concentration	Unbound drug concentration	
	K. oxytoca	Isolate no. 92 [$bla_{OXY-6-4}$ (intrinsic gene)]	≤ 0.015	Susceptible (CLSI)				
	M. morganii	Isolate no. 65 [aac(3)-IId, bla_{DHA-9} (intrinsic gene), aadA5, aph(3′)-Ia]	0.06	Susceptible (CLSI)				
Imipenem	*P. aeruginosa*	WT PAO1 (K767)	1.0 (CLSI)	Susceptible (CLSI)	ND	45% $T_{>MIC}$	40% $fT_{>MIC}$	[68]
	P. aeruginosa	Isogenic K767 + (overexpressing the MexA-MexB-OprM efflux systems)	1.0 (CLSI)	Susceptible (CLSI)	ND	30% $T_{>MIC}$	40% $fT_{>MIC}$	
	P. aeruginosa	Isogenic ΔK767 (MexA-MexB-OprM deleted pumps)	1.0 (CLSI)	Susceptible (CLSI)	ND	37% $T_{>MIC}$	40% $fT_{>MIC}$	
Ciprofloxacin	*P. aeruginosa*	WT PAO1	0.125 (Etest)	NA	80 mg/kg/day q6 h	ND	$fAUC_{24}$/MIC = 385 fC_{max}/MIC = 60	[67]
Levofloxacin	*P. aeruginosa*	ATCC 27853	0.8 (CLS)	Susceptible (CLSI)	750 mg/kg/day	AUC_{24}/MIC = 157	ND	[65]
	E. coli	Clinical isolate E129	0.25 (CLSI)	Susceptible (CLSI)	10 mg, 30 mg and 40 mg/kg/day q24 h	AUC_{24}/MPC > 20; AUC_{24}/MIC < 18 or > 60	ND	[72]
Tobramycin	*P. aeruginosa*	WT PAO1	1.0 (Etest)	NA	80 mg/kg/day q6 h	ND	$fAUC_{24}$/MIC = 43 fC_{max}/MIC = 19	[67]
	P. aeruginosa	WT PAO1	1.0 (CLSI)[a]	Susceptible (CLSI)[a]	ND	AUC_{24}/MIC ≥ 110.6[e]	ND	[71]

Table 6 (continued)

Test antibiotic(s)	Name of test bacteria	Bacterial strain	Baseline MIC, mg/L (method)	Susceptibility	Outcome of the study to suppress the emergence of resistance			References
					Approximate drug dose to suppress emergence of resistance	PK/PD indices		
						Total drug concentration	Unbound drug concentration	
Plazomicin	*K. pneumoniae*	Isolate no. 557 [aadA2, bla_{TEM-1}, bla_{SHV-11}, aac(6′)-Ib, bla_{KPC-2}, aph(3′)-Ia]	2 (CLSI)	Susceptible (CLSI)	15 mg/kg as a 0.5-h infusion q24 h	$AUC_{24}/MIC \geq 137$	ND	[75]
	K. pneumoniae	Isolate no. 558 [aac(3)-IId, aadA2, bla_{TEM-1}, aph(6)-Ia, bla_{SHV-11}, blaKPC-3, aph(6)-Id]	2 (CLSI)	Susceptible (CLSI)				
	K. pneumoniae	Isolate no. 561 [bla_{TEM-1}, bla_{SHV-11}, aac(3)-IIa, $bla_{CTX-M-15}$, aac(6′)-Ib-cr, bla_{OXA-48}, bla_{OXA-1}, bla_{OXA-30}]	8 (CLSI)	Susceptible (CLSI)				
	K. pneumoniae	Isolate no. 559 [bla_{TEM-1}, bla_{SHV-11}, aac(3)-IIa, $bla_{CTX-M-15}$, aac(6′)-Ib-cr, bla_{OXA-48}, bla_{OXA-1}, bla_{OXA-30}]	16 (CLSI)	Resistant (CLSI)				
	E. coli	Isolate no. 471 [aac(3)-IId, bla_{TEM-1}, EC-6 (intrinsic AmpC)]	4 (CLSI)	Susceptible (CLSI)				
	C. freundii	Isolate no. 38 [blaCMY-48-like (intrinsic gene), aac(6′)-If]	4 (CLSI)	Susceptible (CLSI)				
	K. oxytoca	Isolate no. 92 [$bla_{OXY-6-4}$ (intrinsic gene)]	4 (CLSI)	Susceptible (CLSI)				
	M. morganii	Isolate no. 65 [aac(3)-IId, bla_{DHA-9} (intrinsic gene), aadA5, aph(3′)-Ia]	8 (CLSI)	Susceptible (CLSI)				
Fosfomycin[c]	*P. aeruginosa*	ATCC 27853	4.0 (CLSI)	Susceptible (CLSI)	ND	$AUC_{24}/MPC > 10$ 70% $T_{>MPC}$	ND	[74]
	E. coli	ATCC 25922	2.0 (CLSI)	Susceptible (CLSI)				

Table 6 (continued)

Test antibiotic(s)	Name of test bacteria	Bacterial strain	Baseline MIC, mg/L (method)	Susceptibility	Outcome of the study to suppress the emergence of resistance			References
					Approximate drug dose to suppress emergence of resistance	PK/PD indices		
						Total drug concentration	Unbound drug concentration	
Tigecycline	*K. pneumoniae*	Isolate no. 558 [aac(3)-IId, aadA2, bla_{TEM-1}, aph(6)-Ia, bla_{SHV-11}, bla_{KPC-3}, aph(6)-Id]	1.0 (CLSI)	Susceptible (CLSI)	50 mg q12 h	ND	$fAUC_{24}/MIC \geq 13$	[75]
	K. pneumoniae	Isolate no. 561 [bla_{TEM-1}, bla_{SHV-11}, aac(3)-IIa, $bla_{CTX-M-15}$, aac(6′)-Ib-cr, bla_{OXA-48}, bla_{OXA-1}, bla_{OXA-30}]	2.0 (CLSI)	Susceptible (CLSI)				
	E. coli	Isolate no. 471 [aac(3)-IId, bla_{TEM-1}, EC-6 (intrinsic AmpC)]	≤ 0.06 (CLSI)	Susceptible (CLSI)				
	C. freundii	Isolate no. 38 [blaCMY-48-like (intrinsic gene), aac(6′)-If]	0.5 (CLSI)	Susceptible (CLSI)				
	K. oxytoca	Isolate no. 92 [$bla_{OXY-6-4}$ (intrinsic gene)]	0.12 (CLSI)	Susceptible (CLSI)				

B. fragilis Bacteroides fragilis, *C. freundii* Citrobacter freundii, *E. cloacae* Enterobacter cloacae, *E. coli* Escherichia coli, *K. pneumonia* Klebsiella pneumoniae, *K. oxytoca* Klebsiella oxytoca, *P. aeruginosa* Pseudomonas aeruginosa, *M. morganii* Morganella morganii, $fAUC_{24}$ area under the free-drug concentration-time curve in a 24-h interval, *ATCC* American Type Culture Collection, *CLSI* Clinical and Laboratory Standards Institute, $fT_{>MIC}$, percentage of time of the dosing interval during which free-drug concentrations remained above the MIC for the corresponding strain, *MIC* minimum inhibitory concentration, *MPC* mutant prevention concentration, *NA* not available, *ND* not determined, *PK/PD* pharmacokinetic/pharmacodynamic, *qxh* every × hours, *WT* wild type

[a]MIC was determined by National Committee for Clinical Laboratory Standards (NCCLS) currently known as CLSI

[b]MIC determination guideline (CLSI/EUCAST/Etest) was not mentioned in the study

[c]MIC of fosfomycin was determined by supplementation with 25 mg/L of glucose-6-phosphate (G6P) in medium

[d]MIC of ceftazidime was determined in presence of 4 mg/L avibactam [70]

[e]Louie et al. [71] reported AUC/MIC ratio of tobramycin from epithelial lining fluid (ELF)

3.3.3 Fluoroquinolones

AUC/MIC and AUC/MPC were commonly described PK/PD ratios associated with the suppression of emergence of resistance for fluoroquinolones (Table 5). In vitro studies for ciprofloxacin conducted for 24–72 h have reported that an AUC_{24}/MPC of between 11 and ~ 58 is required to suppress the emergence of resistance against *E. coli*, *K. pneumoniae* and *P. aeruginosa* isolates. The AUC_{24}/MIC ratio associated with suppression of resistance varies from 300 to 1400, with no apparent relationship with the AUC/MPC ratio or the bacterial species. On the other hand, a mouse lung infection model study by Maciá et al. [67] reported that a ciprofloxacin AUC_{24}/MIC ratio of 385 prevented the emergence of resistance against a wild-type *P. aeruginosa* isolate (MIC 0.125 mg/L) (Table 6). However, that study also demonstrated that the same ciprofloxacin exposure failed to suppress the emergence of resistance of a hypermutable *P. aeruginosa* strain (MIC 0.125 mg/L). Additionally, a clinical study reported that a higher AUC_{24}/MIC ratio of 582 suppressed the emergence of resistance of susceptible *E. coli*, *Enterobacter cloacae*, *Haemophilus influenzae* and *Serratia marcescens* in patients (Table 7) [76].

3.3.4 Tetracyclines

As shown in Table 5, only one preclinical dynamic two-compartment in vitro study, conducted by Alfouzan et al. [53], has determined the relationship between minocycline exposure and suppression of emergence resistance of *A. baumannii*. This study suggested that an unbound AUC_{24}/MIC ratio of 20–25 was required to suppress the emergence of resistance against three *A. baumannii* isolates (MICs 0.5, 3 and 4 mg/L).

3.3.5 Polymyxins

A literature search conducted for this review identified only two preclinical in vitro studies investigating polymyxin B (Table 5) [30, 43]. An in vitro dynamic HFIM study by Tam et al. [30] suggested that a polymyxin B dose of 20 mg/kg body weight (AUC_{24}/MIC ~ 808) administered twice daily, which is approximately eightfold the current recommended doses, suppressed the emergence of polymyxin B resistance in a wild-type *P. aeruginosa* (MIC 1 mg/L), but failed to suppress the emergence of resistance in three other carbapenem-resistant *P. aeruginosa* clinical isolates (MIC ranged from 0.5 to 1 mg/L). On the other hand, a dynamic one-compartment in vitro study by Hagihara et al. [43] reported that an unbound AUC_{12}/MIC ratio of ~ 8 at a simulated twice-daily polymyxin B dose of 1 mg/kg was required to suppress the emergence of polymyxin resistance in three clinical isolates of carbapenem-resistant *A. baumannii* (MICs 1 mg/L).

3.3.6 Fosfomycin

The likely PK/PD ratio to best describe fosfomycin exposures required to suppress emergence of resistance remains unknown. As shown in Table 6, a preclinical rabbit tissue cage infection model study by Pan et al. [74] suggested that an AUC_{24}/MPC ratio of > 10 prevented the emergence of resistant bacteria against laboratory reference strains of *P. aeruginosa* American Type Culture Collection (ATCC) 27853 (MIC 4 mg/L) and *E. coli* ATCC 25922 (MIC 2 mg/L). Conversely, resistance was identified in all 15 rabbits for both *P. aeruginosa* and *E. coli* when the $T_{>MPC}$ was < 70%. One in vitro dynamic HFIM study by Docobo-Pérez et al. [47] identified a fosfomycin AUC_{24}/MIC ratio of ≥ 3136 suppressed the resistant subpopulation of a susceptible CTX-M-15-producing *E. coli* (MIC 1 mg/L) clinical isolate. In contrast, this study also reported that another CTX-M-15-producing *E. coli* isolate with the same MIC (MIC 1 mg/L) was not suppressed by a similar fosfomycin exposure. On the other hand, a dynamic one-compartment model study by VanScoy et al. [48] suggested that a new PK/PD index, the percentage of the dosing interval that the fosfomycin concentrations remained above the resistance inhibitory concentration (RIC; $f\%T_{>RIC}$), was a better predictor to describe the exposure required for the suppression of emergence of resistance (Table 5). According to their study, a dose ≥ 2 g every 6 h suppressed the emergence of one susceptible *E. coli* ATCC strain (MIC 1 mg/L) and two *E. coli* clinical isolates (MIC for both isolates 1 mg/L) when the $\%fT_{>RIC}$ was more than 32.8.

4 Discussion

Our systematic review, based on 56 preclinical (in vitro and in vivo) and 2 clinical studies, details the antibiotic exposures reported to suppress the emergence of antibiotic resistant Gram-negative bacteria. The results highlight the potential for intraspecies variability of antibiotic exposures required for suppression of resistance that may be independent of the MIC.

The included preclinical studies in this systematic review have reported that the β-lactam exposures of fC_{min}/MIC ≥ 6 achieved by intermittent infusion suppressed the emergence of resistance of highly susceptible isolates [29, 40, 49, 54, 58] and with lower initial inoculum (~ 10^4 CFU/mL) [40]. However, the preclinical study has also shown that resistance emergence to β-lactam antibiotics may occur with an exposure less than a C_{min}/MIC of 4 against the clinically relevant bacterial densities as high as ~ 10^8 CFU/ml [58] frequently encountered in patients with ventilator-associated pneumonia (VAP) [138]. In contrast, the exposure needed for optimal clinical cure varies between > 45% $fT_{>MIC}$

Table 7 Clinical studies of antibiotic exposures and PK/PD indices for suppression of resistance emergence against Gram-negative bacteria

Test antibiotics	Source of isolates	Name of bacteria	Baseline MIC, mg/L (method)	Susceptibility (method)	Outcome of the study to suppress the emergence of resistance			References
					Drug dose to suppress emergence of resistance	PK/PD indices		
						Total drug concentration	Free drug concentration	
Cefmenoxime	Tracheal aspirates	*E. coli*	0.5 (CLSI)[a]	Susceptible (CLSI)[a]	1–2 g q4 h or q6 h	AUC_{24}/MIC = 668	ND	[76]
		K. pneumoniae	1.0 (CLSI)[a]	Susceptible (CLSI)[a]				
		P. mirabilis	3.1 (CLSI)[a]	Susceptible (CLSI)[a]				
		H. influenzae	ND	NA				
Ceftazidime	Tracheal aspirates	*E. cloacae*	8.2 (CLSI)[a]	Susceptible (CLSI)[a]	1–2 g q8 h or q12 h	AUC_{24}/MIC = 5303	ND	[76]
		E. coli	0.2 (CLSI)[a]	Susceptible (CLSI)[a]				
		H. influenzae	0.4 (CLSI)[a]	Susceptible (CLSI)[a]				
		P. mirabilis	0.1 (CLSI)[a]	Susceptible (CLSI)[a]				
Ciprofloxacin	Tracheal aspirates	*E. cloacae*	0.02 (CLSI)[a]	Susceptible (CLSI)[a]	200–300 mg q12 h 400 mg q8 h or q12 h	AUC_{24}/MIC = 582	ND	[76]
		E. coli	0.01 (CLSI)[a]	Susceptible (CLSI)[a]				
		H. influenzae	0.01 (CLSI)[a]	Susceptible (CLSI)[a]				
		S. marcescens	0.06 (CLSI)[a]	Susceptible (CLSI)[a]				
	Any site of infection with *P. aeruginosa*	*P. aeruginosa*	≤ 0.5[b]	NA		$AUIC_{24}$/MIC > 110	ND	[77]

E. cloacae Enterobacter cloacae, *E. coli* Escherichia coli, *H. influenza* Haemophilus influenza, *K. pneumoniae* Klebsiella pneumoniae, *P. aeruginosa* Pseudomonas aeruginosa, *P. mirabilis* Proteus mirabilis, *S. marcescens* Serratia marcescens, AUC_{24} area under the drug concentration-time curve in a 24-h interval, $AUIC_{24}$ area under the inhibitory concentration-time curve in a 24-h interval, *CLSI* Clinical and Laboratory Standards Institute, *MIC* minimum inhibitory concentration, *NA* not available, *ND* not determined, *PK/PD* pharmacokinetic/pharmacodynamic, *qxh* every × hours

[a]MIC of the strain was determined by the National Committee for Clinical Laboratory Standards (NCCLS) method, currently known as the CLSI

[b]The method for MIC determination was not described

[78] and a C_{min}/MIC ≥ 12 [79–82]; however, this is likely dependent on the infectious type and patient illness severity [83]. Thus, the antibiotic dose to suppress the emergence of β-lactam antibiotic resistance for most patients is higher than that required for clinical effect [84–91]. The multicentre Defining Antibiotic Levels in Intensive Care Patients (DALI) study highlights the significant interpatient variability of β-lactam antibiotic pharmacokinetics in the critically ill patient population, with only 60.4% of patients with currently used dosing regimens achieving 100% $fT_{>MIC}$ [92]. Current pharmacokinetic models based on a limited number of patients would suggest that empiric dosing regimens for many β-lactam antibiotics are inadequate to suppress the emergence of resistance. The dose of meropenem, piperacillin/tazobactam and cefepime, for a patient with a creatinine CL of ~ 90 mL/min/1.73 m^2, would need to be increased to 1 g administered 6-hourly, 4/0.5 g administered 4-hourly, and 2 g administered 6-hourly, respectively, to meet the minimum exposures required to suppress the emergence of resistance [84–91]. However, even these doses may not achieve the exposures required to suppress the emergence of resistance in patients infected with higher MIC pathogens. The COMParative Activity of Carbapenem Testing (COMPACT) study highlights that the carbapenem MIC of infectious pathogens for patients in intensive care is higher than for other patients. In addition, due to altered

pharmacokinetics present in critically ill patients, the antibiotic exposure required for both clinical effect and suppression of emergence of resistance is higher as a result of reduced susceptibility of bacteria [93]. Although the higher doses required to suppress the emergence of resistance raises the concern for potential toxicity, the antibiotic exposure required for toxicity is generally high (piperacillin C_{min} ~ 361 mg/L [94–96], cefepime $C_{min} \geq 22$ mg/L [97] and meropenem $C_{min} \geq 64$ mg/L).

There are conflicting results with the aminoglycoside exposure required to suppress the emergence of resistance. A C_{max}/MIC ratio of between 20 (amikacin administered once daily against *A. baumannii*) and 32 (gentamicin administered twice daily against *P. aeruginosa*) have been reported to suppress the emergence of resistance [34, 55]. Moreover, a C_{max}/MIC ratio of 15 (amikacin administered once daily) was associated with microbiological success in the group of patients with VAP [98]. In contrast, a lower C_{max}/MIC of 8–10 has been shown to improve clinical cure rates in patients with nosocomial pneumonia [99], urinary tract infection, lower respiratory tract infection, cutaneous infection, and intra-abdominal infection [100]. On the other hand, an AUC_{24}/MIC ratio of 110 in a murine pneumonia model has also been associated with the suppression of emergence of resistance [71]. This is similar to the AUC_{24}/MIC of 120 associated with improved clinical cure in patients with *P. aeruginosa* bacteraemia [101]. Thus, it would appear that the exposure required to suppress the emergence of antibiotic resistance in vitro is higher than that required for clinical efficacy. Moreover, to adequately achieve target peak drug concentrations, the recommended weight-based 7 mg/kg of tobramycin and gentamicin once-daily regimen was based on PK data derived from a general patient population for the treatment of Gram-negative infections [102, 103]. As a result, current aminoglycoside once-daily dosing regimens may not achieve the exposure required for clinical cure in critically ill patients due to differences in the PK, as shown by Rea et al. [104]. A study by Roger et al. [105] in 63 ICU patients with severe sepsis reported that increasing the dose to 8 mg/kg did not have an appreciable impact to increase the rate of PK/PD target attainment (the rate of target attainment was 100%). However, this study did not determine the infecting pathogen MIC in most cases, and used the EUCAST breakpoint of *P. aeruginosa* for assessing the C_{max}/MIC ratio [105].

Fluoroquinolone resistance emergence is thought to be primarily related to *de novo* mutations. Since concentrations above the MPC suppress selective proliferation of first-step mutants, the MPC may appropriately describe the concentration of a fluoroquinolone that will suppress the emergence of resistance [106, 107]. Fluoroquinolone exposures within the MSW, the concentration range between the MIC and MPC, have been shown to promote resistance emergence [107]. Thus, fluoroquinolone dosing should aim to minimize the time the concentration remains within the MSW to minimize the risk of amplifying resistant bacterial populations. A pharmacodynamic target fT_{MSW} of < 20% is associated with suppression of emergence of resistance [106] that is clinically achievable; an intravenous ciprofloxacin dose of 400 mg administered three times daily would likely be sufficient to suppress the emergence of resistance against a bacterial isolate with an MIC of ≤ 0.125 mg/L for most patients [108–110].

The suppression of polymyxin B resistance emergence against carbapenem-resistant isolates has been described for *A. baumannii* (AUC_{24}/MIC ~ 80) [43], but not for *P. aeruginosa* with an AUC_{24}/MIC exposure > 800 [30]. Thus, targeting the exposure required for optimal bactericidal activity (AUC_{12}/MIC > 50) may also suppress the emergence of resistance against *A.* baumannii [111]. This is clinically achievable with polymyxin B doses of 1.5 mg/kg administered twice daily [112]; however, this may be limited by nephrotoxicity that may occur with daily doses > 250 mg [113]. Polymyxin B monotherapy may be insufficient to suppress the emergence of resistance when used to treat *P. aeruginosa* infections. Importantly, no dosing regimen of colistin has been shown to suppress the emergence of resistance, which may be related to the slow conversion of the prodrug to the active compound [114, 115].

A fosfomycin exposure of an AUC_{24}/MIC ≥ 3136 has been shown to suppress the emergence of resistance for *E. coli* and *E. cloacae* isolates with an MIC ≤ 8 mg/L. With a breakpoint of 8 mg/L, it may be possible to treat and prevent the emergence of resistance for systemic infections in most patients who receive a dose of 8 g administered three times daily [116], or to treat a urinary tract infection with a single 3 g oral dose [60]. However, fosfomycin resistance may emerge during treatment for *K. pneumoniae* or non-fermenting Gram-negative bacterial infections.

Taken together, the PK/PD targets required to suppress the emergence of resistance are higher than that required for clinical efficacy; however, existing data on exposures required to suppress resistance are confounded by various factors. First, many studies determining the exposure required to suppress the emergence of resistance have been conducted in vitro against high bacterial burdens of ~ 1×10^8 CFU/mL. This may reflect certain infectious syndromes such as VAP [16], but not necessarily a primary bacteraemia that may have a bacterial burden of up to 1×10^4 CFU/mL [117]. The bacterial burden is a key consideration given that the probability of a pre-existing resistant subpopulation increases with a larger bacterial burden. Second, the lack of an immune response in in vitro studies limits the potential application to clinical practice. Reducing the bacterial burden to below 1×10^5 CFU/mL, as demonstrated in a murine thigh infection [118] and a pneumonia

[119] model, may result in bacterial CL over 24–48 h. Thus, antibiotic exposures required to suppress the emergence of resistance in vivo may only require the bacterial burden to be reduced to below the threshold for immune CL. However, bacteria also develop mechanisms to evade the host immune response by modulating immune signalling [120] and forming biofilms [121]. Lastly, the antibiotic exposure required for the perceived suppression of emergence of resistance was less for experiments with a duration < 72 h compared with longer durations. This observation may be in keeping with a study of patients with VAP where a treatment duration of 15 days was associated with an increased risk of resistance emergence compared with 8 days of therapy (42.1% vs. 62.3%; $p = 0.04$) [122]. Moreover, critically ill patients with *P. aeruginosa* infections receiving > 15 days of meropenem (OR 10, 95% CI 1.98–551), piperacillin/tazobactam (OR 4.7, 95% CI 1.8–12.4), ciprofloxacin (OR 14.5, 95% CI 2.8–75) or ceftazidime (OR 2.6, 95% CI 1.1–6) were at an increased risk of emergence of resistance [123].

Nevertheless, there are some limitations in our included studies. First, there was a high degree of experimental design heterogeneity among the included studies, such as different initial bacterial inoculums between studies (e.g. 10^5–10^8 CFU/mL), differing experimental durations (e.g. < 24–240 h), and different pharmacokinetic simulations performed. Thus, it was difficult to draw a definite conclusion on the PK/PD indices or required antibiotic exposures for suppression of the emergence of resistance. Second, preclinical studies have mostly used susceptible bacterial strains with a low MIC that may not be representative of that bacterial species. However, a maximum effect (E_{max}) model revealed that the less susceptible strains displayed lower E_{max} and higher half maximal effective concentration (EC_{50}) for tobramycin effect against *P. aeruginosa* [124]. Third, bacterial growth conditions with the idealized laboratory conditions are extraordinarily different from growth within patients. Thus, it is not unexpected that there are evolved genomic differences between laboratory reference strains and corresponding clinical isolates [125, 126]. Fourth, few genomic data were available for bacterial strains that have been used for preclinical studies. Nonetheless, this represents current clinical practice where bacterial genomic data are not available for routine patient care. Last, we did not include in vivo studies that described the emergence of antibiotic resistance in anatomical sites distinct from the infecting site (e.g. the impact of antibiotic administration on the gastric microbiota). This may be an important consideration for future infection with a resistant organism; however, it is unclear how improved dosing regimens of systemically administered antibiotics may reduce the risk of resistance emergence in different anatomical sites where commensal bacteria may colonize [127, 128].

Due to heterogeneity of the included studies in this systematic review, no clear guidelines for clinical targets that should be used to suppress emergence of resistance can be drawn from the current data. As such, we believe that the following investigations should be prioritized for future research: (1) preclinical model testing of whether PK/PD targets associated with suppression of emergence of resistance remain accurate in bacterial strains with higher MICs; (2) preclinical studies using suboptimal PK/PD exposures and the correlation of phenotypic emergence of resistance with genomic data; and (3) clinical and bacteriological outcome data associated with achieving the aforementioned PK/PD targets associated with suppression of emergence of resistance.

5 Conclusions

This systematic review found that the antibiotic exposures for various classes of antibiotics reported to suppress the emergence of Gram-negative bacteria resistance were generally higher than exposures achievable by recommended antibiotic dosing regimens for clinical cure: β-lactam, C_{min}/MIC ≥ 4; aminoglycosides, C_{max}/MIC ratio ≥ 20; fluoroquinolones, AUC_{24}/MPC ≥ 35; tetracyclines, AUC_{24}/MIC ratio ≥ 50; polymyxin B, AUC_{24}/MIC ≥ 808; and fosfomycin, AUC_{24}/MIC ≥ 3136. In addition, the use of high antibiotic dosing that targets the thresholds required to suppress the emergence of resistance should be balanced with the potential risk for concentration-dependent adverse events. Optimization of alternative dosing regimens, such as the use of prolonged or continuous infusions of β-lactam antibiotics, should be considered to improve the probability of achieving the required antibiotic exposure to attain PK/PD indices for suppression of emergence of resistance; however, factors such as bacterial burden, MIC, and altered pharmacokinetics should be considered for optimization purposes.

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Compliance with Ethical Standards

Conflict of interest Chandra Datta Sumi, Aaron J. Heffernan, Jeffrey Lipman, Jason A. Roberts, and Fekade B. Sime have no conflicts of interest to declare.

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