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Review

Intrapulmonary pharmacokinetics of antibiotics used to treat nosocomial pneumonia caused by Gram-negative bacilli: A systematic review

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ABSTRACT

Background: Knowledge of antibiotic concentrations achievable in the epithelial lining fluid (ELF) will help guide antibiotic dosing for treating patients with Gram-negative bacillary ventilator-associated pneumonia (VAP).
Objective: To compare: (1) the ELF:serum penetration ratio of antibiotics in patients with pneumonia, including VAP, with that in healthy study participants; and (2) the ELF and/or tracheal aspirate antibiotic concentrations following intravenous and nebuliser delivery.
Methods: Web of Science, EMBASE and PubMed databases were searched and a systematic review undertaken.
Results: Fifty-two studies were identified. ELF penetration ratios for aminoglycosides and most β-lactam antibiotics administered intravenously were between 0.12 and 0.57, whereas intravenous colistin may be undetectable in the ELF. In contrast, estimated mean fluoroquinolone ELF penetration ratios of up to 1.31 were achieved. Importantly, ELF penetration ratios appear reduced in critically ill patients with pneumonia compared with in healthy volunteers receiving intravenous ceftazidime, levofloxacin and fosfomycin; thus, dose adjustment is likely to be required in critically ill patients. In contrast to the systemic administration route, nebulisation of antibiotics achieves high ELF concentrations. Nebulised 400 mg twice-daily amikacin resulted in a median peak ELF steady-state concentration of 976.01 mg/L (interquartile range 410.3–2563.1 mg/L). Similarly, nebulised 1 million international units of colistin resulted in a peak ELF concentration of 6.73 mg/L (interquartile range 4.80–10.10 mg/L).
Conclusion: Further pharmacokinetic studies investigating the mechanisms for ELF penetration in infected patients and healthy controls are needed to guide antibiotic dosing in VAP and to determine the potential benefits of nebulised therapy.

1. Introduction

Ventilator-associated pneumonia (VAP), a subset of hospital-acquired pneumonia (HAP), affects between 17% and 38% of critically ill patients requiring mechanical ventilation, with an attributable mortality of approximately 13%, which may be reduced by timely recognition and appropriate antibiotic therapy [1–4]. Current guidelines formulated by the Infectious Diseases Society of America and the American Thoracic Society recommend that while the choice of empirical therapy is influenced by the local hospital epidemiology of healthcare-associated pathogens, it should also include agents active against *Staphylococcus aureus* (or methicillin-resistant *S. aureus* [MRSA] if the local prevalence is >10%) and *Pseudomonas aeruginosa* [1,5]. Importantly, as identified in a recent meta-analysis, patients with VAP caused by Gram-negative bacilli have an increased mortality compared with those who are infected with other pathogens (odds ratio [OR] 1.71; 95% confidence interval [CI] 1.09–2.68 P=0.02) [6]. Similar findings were shown in a randomised controlled trial (RCT) where non-fermenting

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Abbreviations

AUC/MIC	area under the concentration versus time curve to MIC ratio
BAL	bronchoalveolar lavage
CI	confidence interval
C_{max}/MIC	maximum drug concentration to MIC ratio
CMS	colistin methanesulfonate
ELF	epithelial lining fluid
EUCAST	European Committee on Antimicrobial Susceptibility Testing
HAP	hospital-acquired pneumonia
ICU	intensive care unit
$\%T_{>MIC}$	percentage of the dosing interval that the total drug concentration exceeds the minimum inhibitory concentration
$\%fT_{>MIC}$	percentage of the dosing interval that the free drug concentration exceeds the minimum inhibitory concentration
ISF	interstitial fluid
MIC	minimum inhibitory concentration
MIU	million international units
PK/PD	pharmacokinetic/pharmacodynamics
RCT	randomised controlled trial
VAP	ventilator-associated pneumonia

Gram-negative bacilli, mainly *P. aeruginosa*, were associated with an increased 28-day mortality (OR 2.18; 95% CI 1.24–3.82) [7]. These results may reflect sub-therapeutic antibiotic exposures at the site of infection in VAP, which is the epithelial lining fluid (ELF) on the internal surface of the alveolar pneumocyte membrane [8,9]. The ELF penetration ratio is the antibiotic concentration in the ELF relative to plasma or serum exposure. However, the methods used to collect ELF or the surrounding interstitial fluid (ISF) can prove challenging and may influence how antibiotic concentration results are interpreted [9]. Other than for sputum, these methods are invasive and include bronchoalveolar lavage (BAL) [10,11], whole lung tissue homogenates [12], and lung microdialysis methods [13]. Moreover, the ELF penetration ratios may be defined by single point comparisons between the antibiotic concentration obtained simultaneously in the ELF and plasma or serum, or by the area under the concentration-time curve (AUC) in both the ELF and the plasma or serum that describes the average antibiotic exposure over the dosing interval. Although subject to interpatient variability, the ELF penetration ratio provides an approximate antibiotic concentration in the ELF should the plasma or serum concentration be known, potentially enabling clinicians to optimise dose selection. However, choosing such a dosing regimen for the critically ill can be challenging because of altered antibiotic pharmacokinetics and increased risk of infection with pathogens with increased minimum inhibitory concentrations (MIC) to antibiotics [14,15]. These factors must be considered in the context of antibiotic pharmacokinetic/pharmacodynamic (PK/PD) ratios.

As antibiotics cannot be titrated to clinical effect, likely therapeutic antibiotic exposures are defined by PK/PD ratios that relate both the antibiotic concentration-time profile and the MIC of the pathogen [14]. These ratios include: the percentage of the dosing interval that the total or unbound antibiotic concentration exceeds the MIC of the pathogen ($\%T_{>MIC}$ or $\%fT_{>MIC}$, respectively – e.g. β-lactam antibiotics), the maximum free and total antibiotic concentration to MIC ratio (fC_{max}/MIC and C_{max}/MIC, respectively – e.g. aminoglycosides) and the antibiotic concentration AUC (reflecting total antibiotic exposure) to MIC ratio (AUC/MIC – e.g. fluoroquinolones, tigecycline, colistin and fosfomycin). However, there is limited clinical evidence to support antibiotic dosing strategies designed to achieve PK/PD targets in the ELF. Nevertheless, it is plausible that attaining these targets could contribute positively to improved patient outcomes [16]. In the absence of well described and robust pharmacokinetic data to guide appropriate antibiotic regimens, inadequate dosing is likely to occur and contribute to both treatment failure and emergence of antibiotic resistance.

Our overall aim was to conduct a systematic review to identify the antibiotic concentration achievable in the ELF that may help clinicians prescribe optimal antibiotic dosing regimens when treating patients with Gram-negative bacillary VAP. The objectives were therefore to compare: (1) the ELF:serum penetration ratio of antibiotics used to treat Gram-negative bacillary pneumonia, including VAP, in critically ill patients with that in healthy study participants; and (2) the ELF and/or tracheal aspirate antibiotic concentrations following intravenous and nebuliser delivery.

2. Methods

2.1. Data sources

The Web of Science, EMBASE and PubMed databases were systematically searched from January 1995 until 31 March 2018. The keyword searches were:

((pneumonia) OR (ventilator*) OR (epithelial lining fluid) OR (alveolar lining fluid)) AND (pharmacokinetic*) AND ((aminoglycoside*) OR (amikacin*) OR (sisom*) OR (isepam*) OR (tobram*) OR (gentam*) OR (netilm*) OR (plazom*) OR (streptom*) OR (kanam*) OR (arbekacin) OR (beta-lactam) OR (beta-lactams) OR (*lactam*) OR (penicillin*) OR (ampicillin) OR (amoxycillin*) OR (amoxicillin*) OR (piperacillin*) OR (ticarcillin*) OR (carbapenem) OR (meropenem) OR (ertapenem) OR (doripenem) OR (imipenem*) OR (biapenem) OR (panipenem) OR (cephalosporin) OR (cefazolin) OR (cephazolin) OR (cephalothin) OR (cefalothin) OR (cephalotin) OR (cefalotin) OR (cefuroxime) OR (ceftriaxone) OR (cefotaxime) OR (cefepime) OR (ceftaroline) OR (ceftolozane) OR (cefpodoxime) OR (ceftazidime) OR (ceftobiprole) OR (aztreonam) OR (fluoroquinolone) OR (quinolone) OR (ciprofloxacin) OR (levofloxacin) OR (moxifloxacin) OR (tigecycline) OR (evracycline) OR (colistin*) OR (polymyxin*) OR (fosfomycin) OR (avibactam) OR (vaborbactam) OR (relebactam) OR (tazobactam) OR (clavulan*) OR (sulbactam)).

Two independent reviewers (A.J.H and F.B.S) performed the literature search, article identification and article quality evaluation. Articles for full review were selected based on the abstracts (Fig. 1).

2.2. Inclusion and exclusion criteria

Regardless of their design, studies investigating currently available antibiotics with a spectrum of activity against Gram-negative bacilli were included if antibiotic concentrations following intravenous or nebulised administration were measured in the ELF, the ISF of lung, or from tracheal aspirate samples of critically ill patients, or from healthy adult human trial participants. Studies that provided pharmacokinetic modelling and simulation data based on previously performed studies were excluded. Pharmacokinetic studies investigating nebulised therapy were also eligible if either serum or plasma concentrations were obtained. Studies investigating patients with cystic fibrosis, chronic obstructive pulmonary disease, bronchiectasis, or pulmonary fibrosis were excluded. Studies involving patients undergoing cardiopulmonary bypass or other extracorporeal oxygenation interventions were also excluded due to the potential influence of the circuit on antibiotic pharmacokinetics.

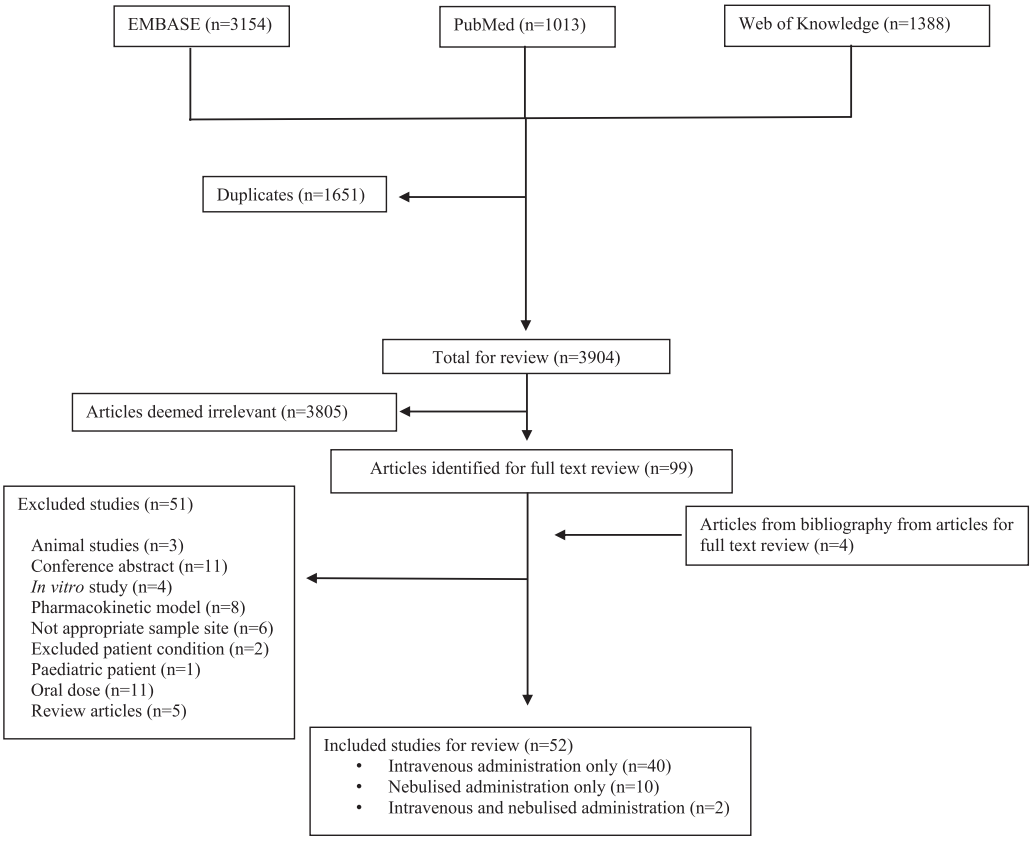

Fig. 1. Preferred reporting items for systematic review and meta-analyses (PRISMA) flow diagram outlining article identification and selection.

Finally, studies involving paediatric patients and those written in languages other than English were also excluded.

2.3. Data extraction

Where available, the following data were extracted from included studies: antibiotic investigated, diagnosis, ELF and serum concentration(s), time of antibiotic administration, route of administration, type of nebuliser device, duration of antibiotic infusion, illness severity score (Acute Physiology and Chronic Health Evaluation [APACHE] II score [17] or Simplified Acute Physiology II [SAP] score [18] or Sequential Organ Failure Assessment [SOFA] score [19]) and number of patients involved in the study.

2.4. Study quality assessment

Study quality was assessed using a modified ClinPK checklist [20]. The checklist has a total of 24 criteria, each worth 1 point. However, two of the criteria pertain to extracorporeal elimination and bioavailability studies and were excluded from quality assessment. The maximum score achieved from the modified ClinPK checklist was therefore 22.

3. Results and Discussion

Fifty-two studies were identified for inclusion in this review (Fig. 1). Forty studies described ELF pharmacokinetics after intravenous antibiotic administration, ten studies described antibiotic concentrations following nebulised administration, and two studies described pharmacokinetics after both intravenous and nebulised dose administration. The data are summarised by drug class as follows.

3.1. β-Lactam antibiotics and β-lactamase inhibitors

This antibiotic class consists of the penicillins, cephalosporins and carbapenems. Despite differences in chemical structure that define these classes, similarly variable ELF penetration ratios have been shown in clinical trials (Table 1 and Supplementary Table 1).

3.1.1. Penicillin ELF penetration following intravenous administration

Variable ELF penetration has been described for piperacillin-tazobactam, a commonly prescribed empirical antibiotic for the treatment of VAP [1]. Piperacillin ELF concentrations in patients with severe HAP receiving a piperacillin-tazobactam dose of 4/0.5 g administered intravenously every 8 h as a 30-min infusion had ELF concentrations that would be below the *P. aeruginosa* European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoint for at least 3 h of the 8-h dosing interval, and thus would be unlikely to meet key PK/PD ratios associated with improved rates of favourable clinical outcomes [23]. Moreover, in a separate study involving piperacillin pharmacokinetic modelling, with an intravenous dose of 4/0.5 g piperacillin-tazobactam administered every 8 h as a 30-min infusion, only 50% and 20% of patients would be expected to achieve 50% $fT_{>MIC}$ or 100% $fT_{>MIC}$, respectively, in the ELF for a *P. aeruginosa* pathogen with an MIC of 16 mg/L, the EUCAST clinical breakpoint [21,59]. Administering the dose as a continuous infusion may increase the $\%T_{>MIC}$ in the ELF. In a separate study, 40% and 60% of patients with a glomerular filtration rate ≥30 mL/min/1.73 m^2 receiving a 12 g or 16 g continuous infusion regimen over 24 h, respectively, met the aggressive PK/PD target ratio of a $\%T_{>MIC}$ of 100% for an isolate with an MIC of 16 mg/L (Table 1, Supplementary Table 1) [24]. However, the ELF penetration ratio was similar between studies in patients receiving a continuous infusion and intermittent infusion dosing regimens (Table 1 and Supplementary Table 1), which indicates that the

Table 1
Epithelial lining fluid penetration ratio for intravenously administered antibiotics.

Author [Ref]	Modified ClinPK score (max score = 22)	Drug	Dosing regimen	Patients (number)	Illness severity score (mean ± SD)	ELF:Serum (mean ± (SD) or median (IQR))
Felton et al. [21]	16	PTZ	4 g Q8H (13 patients), 4 g Q12H (4 patients)	ICU – Pulmonary Infection (n=17)	APACHE II 14.90 (range 3 – 9)	0.49 (range 0.02 – 5.16)
Tomaselli et al. [22]	14	PTZ	4 g single dose, 20-min infusion	ICU – Pulmonary Infection (n=5)	N/A	0.63 ± 0.29
Boselli et al. [23]	12	PTZ	4 g Q8H, 30-min infusion	ICU – VAP (n=10)	SAPSII 30 ± 10	0.57 ± 0.34
Boselli et al. [24]	15	PTZ	12 g CI	ICU – VAP (n=10)$^{\sigma}$	SAPSII 33 – 63	0.46 (IQR 0.29 – 0.62)
			16 g CI	ICU – VAP (n=10)$^{\sigma}$		0.43 (IQR 0.3 – 0.65)
			12 g CI GFR<50 mL/min	ICU – VAP (n=10)$^{\sigma}$		0.39 (IQR 0.31 – 0.48)
			16 g CI GFR<50 mL/min	ICU – VAP (n=10)$^{\sigma}$		0.49 (IQR 0.39 – 0.69)
		TAZ	2 g CI	ICU – VAP (n=10)$^{\sigma}$		0.85 (IQR 0.68 – 1.32)
			2.5 g CI	ICU – VAP (n=10)$^{\sigma}$		084 (IQR 0.5 – 1.05)
			2 g CI GFR<50 mL/min	ICU – VAP (n=10)$^{\sigma}$		0.85 (IQR 0.60 – 00.96)
			2.5 g CI GFR<50 mL/min	ICU – VAP (n=10)$^{\sigma}$		0.65 (IQR 0.63 – 0.80)
Chandorkar et al. [25]	14	CTZ	1.5 g Q8H, 1-h infusion	Healthy (n=25)	N/A	0.48*
		TAZ (CTZ)	500 mg Q8H, 1-h infusion	Healthy (n=25)	N/A	0.44*
		PTZ	4 g Q6H, 30-min infusion	Healthy (n=25)	N/A	0.26*
		TAZ (PTZ)	500 mg Q6H, 30-min infusion	Healthy (n=25)	N/A	0.54*
Boselli et al. [26]	14	CAZ	2 g as a 30-min infusion followed by 4 g CI	ICU – HAP (n=15)	N/A	0.21 ± 0.09
Cousson et al. [27]	15	CAZ	60 mg/kg/day CI	ICU – VAP (n=17)	SAPSII 43	0.42*
			20 mg/kg Q8H, 30-min infusion	ICU – VAP (n=17)	SAPSII 41	0.44*
Nicolau et al. [28]	15	CAZ	2 g Q8H, 2-h infusion	Healthy (n=22)	N/A	0.31*
			3 g Q8H, 2-h infusion	Healthy (n=20)	N/A	0.32*
		AVI	500 mg, 2-h infusion	Healthy (n=22)	N/A	0.32*
			1 g, 2-h infusion	Healthy (n=20)	N/A	0.35*
Klekner et al. [29]	10	CAZ	20 mg/kg Q8H	ICU – HAP (n=4)	N/A	<0.05 (sputum penetration)
		CEF	20 mg/kg Q8H	ICU – HAP (n=5)	N/A	<0.05 (sputum penetration)
Boselli et al. [30]	15	CEF	4 g CI	ICU – HAP (n=20)	SAPSII 43 ± 20	1.04*
Riccobene et al. [31]	20	CFL	600 mg Q12H	Healthy (n=25)	N/A	Range 0.20-0.25
			600 mg Q8H			Range 0.20-0.34
Boselli et al. [32]	15	ERT	1 g Q24H, 1-h infusion	ICU - VAP (n=15)	SAPSII 23 (IQR 18-28)	0.32 (IQR 0.28-0.46)
Conte et al. [33]	18	MER	0.5 g Q8H, 30-min infusion	Healthy (n=10)	N/A	Range 0.32 - 0.53
			1 g Q8H, 30-min infusion	Healthy (n=10)	N/A	Range 0.32 - 0.53
Tomaselli et al. [34]	14	MER	1 g Q8H, 20-min infusion	ICU – HAP (n=7)	N/A	0.41 ± 0.21
Lodise et al. [35]	17	MER	2 g Q8H, 3-h infusion	ICU – VAP (n=39)	APACHEII 19.6 ± 6.9	0.25*
Frippiat et al. [36]	19	MER	1 g Q8H, 30-min infusion	ICU – HAP (n=30)	SAPSIII 73.4 ± 13.7	0.2 ± 0.03
			1 g Q8H, 3-h infusion	ICU – HAP (n=25)	SAPSIII 76.5 ± 13.3	0.29 ± 0.03
Wenzler et al. [37]	18	MER	2 g Q8H, 3-h infusion	Healthy (n=25)	N/A	0.52-1.85
		VAB	2 g Q8H, 3-h infusion			Range 0.44-0.74
Kikuchi et al. [38]	16	BIA	300 mg single 30-min infusion	Healthy (n=6)$^{\sigma}$	N/A	0.19*
			300 mg single 3-h infusion	Healthy (n=6)$^{\sigma}$	N/A	0.20*
Rizk et al. [39]	20	IMP	500 mg (with cilistatin), Q6H, 30-min infusion	Healthy (n=16)	N/A	0.32-0.55
		REL	250 mg Q6H, 30-min infusion			0.32-0.51
Oesterreicher et al. [40]	18	DOR	500 mg Q8H, 1-h infusion	ICU – Pneumonia (n=16)	N/A	0.29*
			500 mg Q8H, 4-h infusion			0.21*
Boselli et al. [41]	17	TOB	7 mg/kg Q24H	ICU – VAP (n=12)	SAPSII 49 ± 11	0.12*
Carcas et al. [42]	15	TOB	TDM adjusted dosing Q8H	ICU – VAP (n=16)	N/A	Range 0.30 – 1.53
Mazzei et al. [43]	13	TOB	300 mg IM single dose	ICU (n=5)	N/A	1.40 ± 0.80
			300 mg IM Q24H	ICU (n=5)	N/A	1.60 ± 0.60
Panidis et al. [44]	16	GEN	240 mg Q24H	ICU – VAP (n=24)	APACHEII 19.1 ± 0.9	0.30-1.14
Santre et al. [45]	16	AMK	15 mg/kg Q24H	ICU – Pneumonia (n=5)	N/A	0.66 – 0.81 (sputum penetration)
			7.5 mg/kg Q12H	ICU – Pneumonia (n=5)	N/A	Range 0.46 – 0.57
Najmededin et al. [46]	17	AMK	20 mg/kg Q24H	ICU – VAP (n=7)	APACHEII 16.1 ± 3.2	0.09 (IQR 0.07-0.31)
Funatsu et al. [47]	17	ARB	200 mg single dose	Healthy	N/A	0.68*
Imberti et al. [48]	16	COL	2 MIU CMS Q8H	ICU – VAP (n=13)	SAPSII 48.2 ± 17.1	0
Markou et al. [49]	Case Report	COL	2.8 MIU CMS Q8H	ICU – VAP (n=1)	N/A	7.42
Boisson et al. [50]	17	COL	2 MIU CMS Q8H	ICU – VAP (n=12)	SAPSII 38 ± 14	Range 6.15-9.87
Matzi et al. [51]	14	FOS	4 g single dose	ICU – Sepsis, healthy lung tissue (n=7)	N/A	0.63 ± 0.31
				ICU – Sepsis, infected lung tissue (n=7)	N/A	0.53 ± 0.31

(*continued on next page*)

Table 1 (*continued*)

Author [Ref]	Modified ClinPK score (max score = 22)	Drug	Dosing regimen	Patients (number)	Illness severity score (mean ± SD)	ELF:Serum (mean ± (SD) or median (IQR))
Conte et al. [52]	16	TIG	100 mg loading dose then 50 mg Q12H, 30-min infusion	Healthy (n=30)	N/A	1.32*
Gotfried et al. [53]	17	TIG	100 mg loading dose then 50 mg Q12H, 30-min infusion	Healthy (n=21)	N/A	1.43-2.41
		OMA	100 mg Q12H for 2 doses, then 100 mg Q24H, 30-min infusion	Healthy (n=42)	N/A	0.96-2.53
Connors et al. [54]	18	EVR	1 mg/kg total body weight Q12H, 1-h infusion	Healthy (n=20)	N/A	1.08*
Boselli et al. [55]	15	LEV	500 mg Q24H	ICU – CAP (n=12)	SAPSII 29 (IQR 27 – 68)	Range 1.18 - 1.31
		LEV	500 mg Q12H	ICU – CAP (n=12)	SAPSII 40 (IQR 30 – 48)	Range 1.12 - 1.27
Conte et al. [56]	18	LEV	1000 mg Q24H	Healthy (n=20)	N/A	2.00-3.31
		LEV	750 mg Q24H	Healthy (n=4)	N/A	4.91*
Rodvold et al. [57]	17	LEV	500 mg Q24H	Healthy (n=12)	N/A	Range 1.53 – 2.58
			750 mg Q24H	Healthy (n=12)	N/A	Range 1.72 – 2.06
Leone et al. [58]	15	MOX	400 mg Q24H	ICU – VAP (n=17)	N/A	Range 0.88 – 1.13

AMK Amikacin; APACHE II Acute Physiology and Chronic Health Evaluation II Score; BIA Biapenem; CAP Community-acquired pneumonia; CAZ Ceftazidime; CEF Cefepime; CFL Ceftaroline; COL Colistin; CI Continuous Infusion; CTZ Ceftolozane-tazobactam; DOR Doripenem; ERT Ertapenem; EVR Evracycline; FOS Fosfomycin; GEN Gentamicin; GFR glomerular filtration rate; HAP Hospital-acquired pneumonia; IMP Imipenem; VAP Ventilator-associated pneumonia; IM Intramuscular; IQR Interquartile range; LEV Levofloxacin; MER Meropenem; min minute; MOX Moxifloxacin; N/A Not available; OMA Omadacycline; PTZ Piperacillin-tazobactam; Q6H every 6 hours; Q8H every 8 hours; Q12H every 12 hours; Q24H every 24 hours; REL Relebactam; Result ± Standard deviation; SAPSII Simplified Acute Physiology Score II; TDM Therapeutic Drug Monitoring; TIG Tigecycline; TOB Tobramycin; VAB Vaborbactam (RPX7009); σ Cross-over study.

* mean without SD reported.

increased ELF exposure in patients receiving a continuous infusion is likely to be a result of sustained, high piperacillin serum concentrations compared with concentrations achieved with intermittent infusion dosing regimens. These data indicate that continuous infusion regimens improve the probability of piperacillin PK/PD target attainment in the ELF; however, even higher doses than 16 g administered over 24 h may be required to minimise the chance of treatment failure in patients infected with high MIC pathogens.

3.1.2. Cephalosporin ELF penetration following intravenous administration

Similar to the other β-lactam antibiotics outlined in Table 1, ceftazidime has variable ELF penetration. Ceftazidime doses of approximately 60 mg/kg administered as a continuous infusion have resulted in mean ELF penetration ratios of between 0.21 [26] and 0.42 [27]. It is thus unlikely to achieve a $\%T_{>MIC}$ of approximately 100% in the ELF for most patients receiving the usual recommended intravenous doses of up to 8 g daily when the infecting pathogen has an MIC equivalent to the *P. aeruginosa* ceftazidime breakpoint of 8 mg/L (Table 1 and Supplementary Table 1) [26–28,59]. On the other hand, cefepime has an increased ELF penetration (~1.04) compared with other β-lactam antibiotics [30]. Thus, when dosed as a 4-g daily continuous infusion, the cefepime $\%T_{>MIC}$ would be 100% for *P. aeruginosa* isolate with an MIC of 8 mg/L, the EUCAST MIC clinical breakpoint [59,60]. The impact of the increased ELF penetration compared with other β-lactam antibiotics for patient outcomes remains unknown but would likely be improved for high MIC pathogens or where dosing adjustment does not overcome the reduced ELF penetration. Ceftaroline is a cephalosporin with activity against *Enterobacterales* and MRSA with similar ELF penetration to that of other cephalosporins [31]. In healthy study participants, the ELF concentration of ceftaroline exceeds the EUCAST *Enterobacterales* breakpoint for approximately 4 h following a 600 mg intravenous dose [31,33]. The potential advantage of this agent is the inclusion of MRSA coverage; however, the lack of activity against *P. aeruginosa* is potentially a disadvantage in the empirical treatment of VAP.

3.1.3. Carbapenem ELF penetration following intravenous administration

Meropenem administered to healthy volunteers as a 1 g dose every 30 min results in an ELF penetration of between 0.19 and 0.53, corresponding with a $\%T_{>MIC}$ in the ELF of 38% for bacterial pathogens with an MIC of 2 mg/L, the EUCAST susceptibility breakpoint for *Enterobacterales* and *P. aeruginosa*; this approximates the minimum $\%T_{>MIC}$ required for improved clinical outcomes (Table 1 and Supplementary Table 1) [33]. Similar ELF penetration ratios have been described for critically ill patients with VAP receiving meropenem, and may be increased with a prolonged 3-h infusion compared with the standard 30-min infusion duration [35,36]. In a critically-ill patient cohort, the prolonged infusion regimen (1 g administered over 3 h) achieved ≥40% $T_{>MIC}$ in the ELF for a pathogen with an MIC ≤0.5 mg/L [36], whereas in healthy volunteers the same dose given as an intermittent infusion achieved an ELF exposure of about 40% $T_{>MIC}$ for a pathogen with an MIC as high as 2 mg/L [33]. For such less susceptible pathogens, the ELF concentrations attained in critically ill patients following dosing regimens as high as 6 g administered over 24 h may not be adequate [61].

3.1.4. β-Lactamase inhibitor ELF penetration following intravenous administration

Avibactam, relebactam and vaborbactam are new β-lactamase inhibitors that are available in combination with ceftazidime, imipenem and meropenem, respectively. The addition of these agents extends the spectrum of carbapenem activity to include many serine carbapenemase-producing organisms [62]. Maintaining β-lactamase inhibitor concentrations above the concentration required to inhibit enzyme activity by 50% (IC_{50}) at the site of infection to ensure maximal enzyme inhibition is key to minimising β-lactam antibiotic degradation. This concept is supported by the suppression of bacterial regrowth after pathogens are exposed to avibactam at concentrations >0.28 mg/L in combination with ceftazidime [63,64]. Avibactam has an ELF penetration ratio similar to ceftazidime, which achieves a concentration in the ELF following a 500-mg dose that is likely to exceed the IC_{50} of target

β-lactamases throughout the dosing interval of 8 h [28,65]. Similar results have been described with vaborbactam and relebactam, which have an approximately equivalent ELF penetration and concentration-time profile as meropenem and imipenem, respectively (Table 1 and Supplementary Table 1) [37,39,65]. This would be expected to result in concentrations sufficient for the inhibition of most relevant carbapenemases at the end of the dosing interval for these drugs [39,65]. However, no study has investigated the ELF penetration of any β-lactamase inhibitor in critically ill patients. Given that the β-lactamase inhibitors, like their associated antibiotics, may have significant inter- and intra-patient pharmacokinetic variability, this may be one factor that requires further investigation to minimise the risk of antibiotic resistance and treatment failure for patients with pneumonia [66].

3.1.5. β-Lactam antibiotic ELF exposure following nebulised administration

One study has investigated plasma exposure following nebulised ceftazidime; however, no ELF concentration data are available (Table 2) [67]. Further research is required to determine the clinical outcome benefits of this method of administration.

3.2. Aminoglycosides

3.2.1. ELF penetration following intravenous administration

Intravenous aminoglycosides penetrate poorly into the ELF with an approximate 12% penetration at the expected serum maximum drug concentration (C_{max}) (Table 1 and Supplementary Table 1) [41,42,44]. In general, the reported low aminoglycoside ELF penetration ratios mean that concentrations in the ELF are unlikely to meet optimal C_{max}/MIC or AUC/MIC ratios of >10 and >80, respectively, which are associated with improved clinical outcomes [78,79]. Furthermore, due to mucin [80], DNA [81] and surfactant [82] binding, the free aminoglycoside concentration available for antibacterial effect may be up to 50% lower than the total concentration reported in most of the studies. The only study that investigated the free concentration of an aminoglycoside (intravenous tobramycin 7 mg/kg) in the ELF, reported a low ELF peak concentration of only 2.7 mg/L with a corresponding serum concentration of 22.4 mg/L; however, this study did not report the total ELF concentration for comparison [41]. A similar low ELF concentration (median 3.6 mg/L) has also been described for amikacin (Table 1 and Supplementary Table 1) [46]. Arbekacin is the newest aminoglycoside with activity against isolates expressing aminoglycoside-modifying enzymes. Compared with other aminoglycosides, the ELF penetration ratio of arbekacin is increased by an average of 47%; however, it is unknown if the ELF penetration is similar in critically ill patients with VAP [47]. No published data were identified by this search for plazomicin.

Impaired aminoglycoside ELF penetration and increased mucin and protein binding locally reduce free ELF concentrations; these factors may contribute to increased mortality rates in patients with Gram-negative bacillary pneumonia treated with intravenous aminoglycoside monotherapy (36.7%) compared with other antibiotics (17.9%) [83].

3.2.2. ELF exposure following nebulised administration

Given the potential limitation of meeting key target site PK/PD ratios with common intravenous doses of aminoglycosides, nebulised administration of these antibiotics has been advocated to maximise the C_{max}/MIC ratio at the infection site with minimal systemic toxicity [84]. Indeed, nebulised administration achieves high ELF concentrations (Table 2). In one study [69], the median steady-state amikacin ELF concentrations following a nebulised dose of 400 mg were approximately 28- to 35-fold higher than that achievable by intravenous administration of conventional once daily doses of 25 to 30 mg/kg [44,85,86]. In a separate study of patients receiving the same nebulised 400 mg amikacin dose via the same nebuliser device, tracheal aspirate concentrations were as high as 16212 mg/L (coefficient of variation 85%) [68]. However, tracheal aspirate concentrations following nebulised administration may overestimate the free antibiotic concentration in the ELF as amikacin ELF concentrations in the involved lung segment obtained by BAL are approximately 64% that of tracheal aspirate concentrations when sampled [69,80]. High and variable tracheal aspirate concentrations have also been reported in other studies (Table 2) and these may result from the different nebuliser systems used in these studies (Supplementary Fig. 1) [87–91].

For a complete discussion of these and other factors relating to aerosol delivery and deposition, which are beyond the scope of this article, the reader is directed to a recent review [92].

Despite these challenges in dose administration, nebulised aminoglycoside administration may improve patient outcomes, without associated systemic adverse events, such as nephrotoxicity. A recent small RCT has shown that nebulised amikacin compared with intravenous amikacin, both combined with piperacillin-tazobactam, improved clinical cure (91.8% vs. 70.2%, P=0.002) and reduced the intensive care unit length of stay (6 vs. 9 days, P=0.01) in postcardiac surgery patients diagnosed with a multidrug-resistant Gram-negative bacillary nosocomial pneumonia [93]. However, similar to another small RCT [94], no difference in mortality was shown [93]. Systemic absorption of inhaled aminoglycosides through the conducting airways and alveolar-capillary barrier is limited, such that relatively higher doses can be administered without an apparent increased risk of systemic toxicity [70,84]. Indeed, nebulised doses of amikacin up to 60 mg/kg have been well tolerated in healthy volunteers and in patients with chronic kidney disease [69–71,74,86]. Evidence from clinical trials with nebulised amikacin to date have not shown an increased risk of nephrotoxicity, which is consistent with the low serum concentrations [67,95–98].

Nebulised administration of aminoglycoside achieves higher ELF concentrations than intravenous administration, and may improve patient outcomes in small studies comparing the method of aminoglycoside administration (Table 1) [93,94]. Moreover, nebulised aminoglycoside administration is likely associated with a reduced risk of nephrotoxicity but increased risk of respiratory complications, such as bronchospasm and hypoxemia, compared with intravenous administration [84]. Thus, the risks and benefits of nebulised therapy need to be considered before instituting treatment for the individual patient.

3.3. Fluoroquinolones

3.3.1. ELF penetration following intravenous administration

No studies conducted thus far have correlated ELF and serum concentrations in patients receiving fluoroquinolones for VAP. However, other lung infections have been studied. Levofloxacin doses of 500 mg administered intravenously once or twice daily in mechanically-ventilated patients with community-acquired pneumonia resulted in ELF:serum ratios >1 [55]. No difference in penetration ratio was observed between 500 mg administered once daily and 500 mg administered twice daily [55]. Similar to other previously described antibiotics, the ELF penetration ratio was reduced in critically ill patients compared with healthy study participants (Table 1 and Supplementary Table 1). These results indicate that fluoroquinolones have a favourable ELF penetration ratio compared with other antibiotics used for treating HAP (Table 1 and Supplementary Table 1). Despite improved ELF penetration and microbiological clearance rates, a meta-analysis did not identify a mortality difference between fluoroquinolones and either

Table 2
Epithelial lining fluid exposure following nebulised antibiotic administration.

Author [ref]	Modified ClinPK score (max score = 22)	Drug	Dosing regimen	Patients	Illness severity score	Serum AUC (mg.hr/L)	Sample timing post-dose	Serum or plasma (mg/L)	ELF (mg/L)	Tracheal aspirate AUC (μg.hr/g) (mean ± SD)
Niederman et al. [68]	15	AMK	400 mg Q12H	ICU – VAP (n=21)	APACHEII 15.7 ± 4.5					Day 1 24034, Day 3 39484$^{\Omega}$ Day 1 41991, Day 361908$^{£}$
			400 mg Q24H	ICU – VAP (n=26)	APACHEII 16.70 ± 7.00					Day 1 20101, Day 3 17332$^{\Omega}$ Day 1 25284, Day 3 25216$^{£}$
Luyt et al. [69]	15	AMK	400 mg Q12H	ICU – VAP (n=30)	N/A	6.15 (IQR 4.73 – 9.57)$^{\Omega}$			976.07 (IQR 410.33 – 2563.12)$^{§\ \Omega}$	
Ehrmann et al. [70]	16	AMK	40 mg/kg single dose	Healthy (n=6)$^{\sigma}$	N/A	49 (IQR 39 – 55)$^{\pi}$				
			50 mg/kg single dose	Healthy (n=6)$^{\sigma}$	N/A	63 (IQR 55 – 67)$^{\pi}$				
			60 mg/kg single dose	Healthy (n=6)$^{\sigma}$	N/A	66 (IQR 50 – 71)$^{\pi}$				
Luyt et al. [71]	16	AMK	400 mg Q12H	ICU – HAP (n=4)	N/A	19.32 (IQR 6.32 – 36.87)$^{\Omega}$			887 (range 406 – 12819)$^{§\ \Omega}$	
Lu et al. [67]	14	AMK	25 mg/kg single daily dose	ICU – *P. aeruginosa* VAP (n=20)	SOFA 3.20 (IQR 2.50 – 7.50)		0.5	8.9 (IQR 5 –11)		
							24	2.4 (1.70 – 5.90)		
		CAZ	15 mg/kg Q3H				0.5	12.10 ± 8.40		
							3	8.10 (IQR 6.00 –12.40)		
Montgomery et al. [72]	12	AMK	100 mg Q24H	ICU - VAP or VAT (n=3)	N/A	555.08 ± 212.79$^{£}$				10181.44 ± 4279.67$^{£}$
			200 mg Q24H	ICU - VAP or VAT (n=6)	N/A	2893.51 ± 1475.52$^{£}$				28549.68 ± 36433.09$^{£}$
			300 mg Q24H	ICU - VAP or VAT (n=7)	N/A	5829.81 ± 1983.49$^{£}$				19280.42 ± 13307.43$^{£}$
			400 mg Q24H	ICU - VAP or VAT (n=4)	N/A	7394.83 ± 2466.32$^{£}$				18420.94 ± 6634.08$^{£}$
Petitcolin et al. [73]	18	AMK	60 mg/kg	ICU – VAP (n=20)	SAPSII 42	23.2 (IQR 6.01 -86.70)$^{£}$				
Stass et al [74]	18	AMK	400 mg Q12H	Mild – Moderate Chronic Renal failure (n=6)	N/A	28.6 ± 6.3	C_{max}	0.94 ± 0.88		
				Severe chronic renal failure (n=6)		103.9 ± 68.7	C_{max}	2.46 ± 1.94		
Boisson et al. [50]	17	COL	2 MIU single dose	ICU – VAP (n=12)	SAPSII 38 ± 14		C_{max}	0.15 – 0.73 mg/L	9.53 – 1137.00 mg/L	Range 100-1000
Boisson et al. [75]	19	COL	0.5 MIU Q8H, 30-min nebulisation	ICU – VAP (n=12)	SAPSII 35 ± 13	0.17 (IQR 0.11-0.22)$^{\theta}$				
Athanassa et al. [76]	16	COL	1 MIU single dose	ICU – VAT (n=20)	APACHEII 15.90 (range 6 – 27)		1	1.20 (IQR 1.10 – 1.40)	6.73 (IQR 4.80 –10.10)	
							4	0.75 (IQR 0.68 –0.95)	3.90 (IQR 2.50 – 60)	
							8	0.31 (IQR 0.29 –0.50)	2 (IQR 1.00 – 3.80)	
Bihan et al. [77]	17	COL	4 MIU in 6 mL	ICU - VAP $^{\sigma}$ (n=8)	N/A	6.6 (IQR 4.3-17.0)				
			4 MIU in 12 mL	ICU - VAP $^{\sigma}$ (n=8)	N/A	6.7 (IQR 3.6-14.0)				
Montgomery et al. [72]	12	FOS	40 mg Q24H	ICU - VAP or VAT (n=3)	N/A			879.49 ± 548.01$^{£}$		6830.67 ± 1603.46$^{£}$
			80 mg Q24H	ICU - VAP or VAT (n=6)	N/A			1828.49 ± 1203.6$^{£}$		13206.33 ± 11797.84$^{£}$
			120 mg Q24H	ICU - VAP or VAT (n=7)	N/A			2994.01 ± 840.41$^{£}$		10409.67 ± 7393.95$^{£}$
			160 mg Q24H	ICU - VAP or VAT (n=4)	N/A			3389.02 ± 789.96$^{£}$		10740.10 ± 7563.37$^{£}$

Result ± Standard deviation; h hour; min minute; N/A Not available; IQR interquartile range; VAP Ventilator-associated pneumonia; VAT Ventilator-associated tracheobronchitis; HAP Hospital-acquired Pneumonia; SAPSII Simplified Acute Physiology Score II; APACHE II Acute Physiology and Chronic Health Evaluation II Score; SOFA Sequential Organ Failure Assessment; § Steady-state; α Bronchial secretion concentrations; σ Cross-over study; OD Once daily; AMK Amikacin; COL Colistin; FOS Fosfomycin; CAZ Ceftazidime; Q3H every 3 hours; Q12H every 12 hours; Q24H every 24 hours; π $AUC_{0-\infty}$; £ AUC_{0-24h}; Ω AUC_{0-12h}; θ AUC_{0-8h}.

imipenem-cilistatin or ceftazidime in the treatment of nosocomial pneumonia [99].

3.3.2. ELF penetration following nebulised administration

No nebulised data for fluoroquinolones in HAP, including VAP, were identified by this systematic review.

3.4. Colistin

3.4.1. ELF penetration following intravenous administration

Colistin is a polymyxin antibiotic for which ELF penetration following intravenous administration has not been studied extensively. One study could not detect colistin in the ELF of critically ill patients with VAP after 2 days of intravenous therapy with a dose of 2 million international units (MIU) of its prodrug, colistin methanesulfonate (CMS), when administered thrice daily (Table 1 and Supplementary Table 1) [48]. Although this study used pooled BAL samples from four collections each after instilling 50 mL of sterile saline, it did not describe how the dilution effect of saline was taken into account. In contrast, accounting for the dilution effect, a case study of a VAP patient treated with an intravenous dose of 2.8 MIU CMS resulted in an ELF penetration ratio of 7.42 [49]. These disparate results may be a result of different methods to account for saline dilution during the BAL, inter-patient variability, another unidentified variable, or a combination of factors. Nonetheless, given the limited studies, it remains unclear whether intravenous colistin consistently penetrates well into the ELF in the majority of patients.

3.4.2. ELF exposure following nebulised administration

Nebulised CMS has been investigated to address the potential uncertainty of colistin ELF penetration. Studies with nebulised CMS doses $\geq$1 MIU have achieved colistin concentrations that exceed the *P. aeruginosa* EUCAST MIC breakpoint [50,59,76]. However, colistin, like the aminoglycosides, binds to mucin (~85–90%); this has not been accounted for by determining the unbound colistin concentrations in any of the previous studies [80]. Despite this, the high colistin ELF concentrations following nebulisation may partly explain the results of a recent meta-analysis comparing a combination of nebulised and intravenously administered colistin with intravenous colistin administration alone, where the combined administration strategy reduced all-cause mortality (OR 0.69, 95% CI 0.50–0.95) and increased clinical response rates (OR 1.81, 95% CI 1.3–2.53, P=0.0005) [100]. Importantly, there was no increased risk of nephrotoxicity for the adjunct strategy compared with intravenous administration alone (OR 1.11, 95% CI 0.69–1.80) [100]. Similar to nebulised aminoglycoside administration, reduced mortality with the combination of nebulised and intravenous colistin must be balanced against a potentially increased risk of respiratory adverse events from nebulised delivery, particularly in hypoxic patients [84].

Overall, given the questionable ELF penetration following intravenous administration and the potential for emergence of polymyxin resistance at concentrations achievable with nebulised dosing, nebulised colistin as an adjunct to intravenous colistin administration should be considered in combination with another active antibiotic [1,101].

3.5.1. ELF penetration following intravenous administration

Few studies have investigated the pharmacokinetics of fosfomycin in the ELF or ISF after intravenous administration in critically ill patients (Table 1 and Supplementary Table 1). One microdialysis study [51] found that fosfomycin ELF penetration in infected lung segments was reduced by approximately 10% compared with healthy segments following a 4-g intravenous bolus dose. No clinical studies have compared outcomes and fosfomycin lung exposure.

3.5.2. ELF exposure following nebulised administration

Nebulised fosfomycin has been investigated as a method to enhance bactericidal activity of fosfomycin. In patients with VAP or ventilator-associated tracheobronchitis, a single daily dose of 40 mg nebulised fosfomycin would likely result in tracheal aspirate AUC exposures exceeding that required for isolates with an MIC of 32 mg/L (Table 2) [72]. Although high amikacin and fosfomycin concentrations are clearly achieved in the ELF following co-administered nebulisation, the clinical impact of this has not been seen. In an RCT of 143 patients, no mortality benefit (24% vs. 17%) or reduction in Clinical Pulmonary Infection Score (day 10, 5.0±3.1 vs. 4.8±3.4, P=0.81) was identified in patients receiving a combination of amikacin 300 mg and fosfomycin 120 mg nebulised twice daily compared with placebo, respectively [95]. However, patients were also prescribed intravenous meropenem and could be enrolled to receive nebulised amikacin and fosfomycin within 72 h of commencing intravenous meropenem, which may result in a potential survivor bias and confound the potential efficacy of the inhaled antibiotic combination.

3.6. Tetracycline-related antibiotics

3.6.1. ELF penetration following intravenous administration

No pharmacokinetic study has investigated tigecycline ELF concentrations in patients with VAP. Studies conducted in healthy volunteers receiving a 100 mg loading dose followed by 50 mg tigecycline twice daily highlight that standard dosing regimens are unlikely to achieve key PK/PD targets associated with improved clinical response in patients with HAP [52,102,103]. In contrast, another study involving healthy subjects [53] showed increased tigecycline ELF penetration. Consistent with this finding is a study showing improved clinical cure rates in patients with VAP receiving a 200 mg loading dose and 100 mg twice-daily maintenance dose [104]. Less is known about the new agent omadacycline. Omadacycline has a comparable ELF penetration ratio to tigecycline; however, the systemic exposure is approximately threefold higher [53]. The relevance of the different pharmacokinetic profile for clinical outcomes remains to be studied.

4. Limitations of ELF PK/PD studies

When interpreting ELF pharmacokinetic data, it is important to consider the technical aspects of obtaining these concentrations [9]. Assessment of ELF antibiotic concentrations is difficult, requiring invasive procedures, such as BAL or microdialysis [9]; thus, intensive repeated sampling may be considered unethical and generally not feasible when BAL techniques are used, so only a single data point may be available per study participant [13]. The single ELF data point may be paired with a plasma antibiotic concentration to describe the ELF penetration. However, as the ELF and plasma concentrations may change at rates independently of each other, the use of a single time point to describe ELF penetration may be biased [105]. Therefore, comparing the ELF and plasma AUC may provide a better assessment of the overall average antibiotic exposure. Further complicating these comparisons is the use of results from several patients to formulate an ELF concentration-time profile that may be used to determine an AUC; however, this is unlikely to reflect the true exposure in the individual patient [42,44]. Results from studies with ELF AUC data are summarised in Fig. 2.

As BAL involves instillation of fluid into the lung, the sample requires a dilution correction, for which urea BAL concentrations are often used [9,106]. This has two key limitations. Firstly, it is unlikely that urea equilibrates with the instilled volume of fluid from the BAL procedure at the same rate as all antibiotics, which under- or over-estimates the true free antibiotic ELF concentration

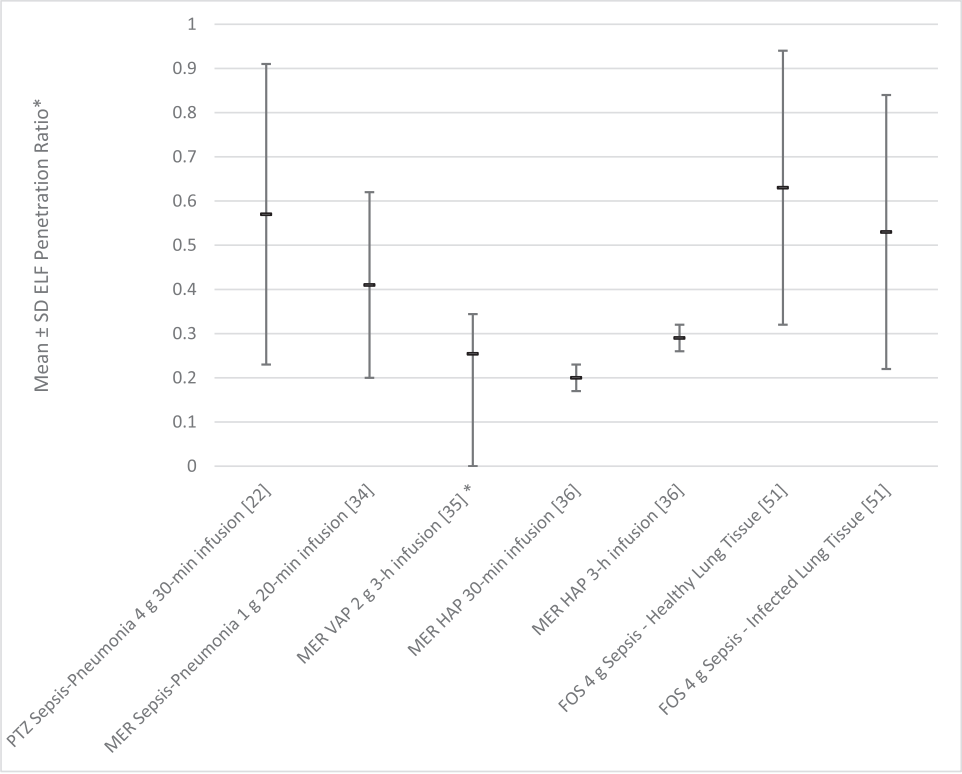

Fig. 2. Epithelial lining fluid penetration ratios following intravenous dosing for antibiotics with area-under-the-curve data.

[106,107]. Nevertheless, urea is the best currently available endogenous marker of dilution due to the reduced variance in diseased and normal lung tissue compared with albumin, another possible marker [108]. Secondly, the site of sampling may be different from the actual site of infection. Standardised anatomical sites, typically the right middle lobe, are often sampled for convenience. However, the site of infection may be at another location with altered antibiotic pharmacokinetics due to altered vascular perfusion [109] and oedema as a result of the inflammatory milieu [110]. Thirdly, studies may use a variety of nebuliser delivery systems (e.g. vibrating mesh or jet) with different or unreported ventilator settings, which can influence the comparability between studies (Supplementary Material Figure 1). Finally, the sample may not reflect the target site; for example, sputum samples and whole tissue homogenates do not reflect the concentration in the ELF [12,45].

4.1. Limitations of antibiotic PK/PD targets to guide dosing

From a clinical perspective, the PK/PD targets for the treatment of VAP have not been extensively studied. Current PK/PD studies in patients with VAP have only studied plasma antibiotic exposures [64]. No studies have yet been performed that correlate antibiotic ELF exposures with clinical outcomes. This is an important distinction as the pneumonic ELF milieu is acidic (pH ~6.48), oedematous [110] and contains macromolecules, such as mucin and surfactant, that may alter the free antibiotic concentration available for bactericidal activity [80,82,110,111]. Moreover, the presence of macromolecules, such as mucin, modulates the immune response and enhances the tolerance of *P. aeruginosa* to tobramycin by inducing biofilm formation [112,113]. These data indicate that the antibiotic exposure associated with optimal patient outcomes in ELF for management of VAP is different to that required in plasma. This is because of the differences in ELF pharmacokinetics and the specific ELF environment that alters the antibacterial effect of antibiotics. Prospective PK/PD studies associating ELF antibiotic exposure and clinical effectiveness are required to determine antibiotic dosing regimens that optimise clinical outcomes.

5. Conclusion

There is limited information on ELF penetration for most antibiotics in patients with HAP, including VAP. Compared with healthy volunteers, critically ill patients with VAP may have an altered pharmacokinetic profile, leading to decreased ELF penetration ratios for most antibiotics discussed in this review. Consequently, current intravenous dosing recommendations are probably inadequate for critically ill patients in whom pathogens with elevated MIC values are frequently encountered [15]. Nebulised therapy may improve antibiotic concentrations in the ELF and a combined approach of intravenous and nebulised therapy may be required. There is an urgent need for improved dosing regimens that optimise known PK/PD ratios in the ELF, and nebulised antibiotics should be considered for antibiotics that have limited or suboptimal ELF penetration when administered systemically.

Until clinical trials are conducted to show the potential clinical utility of improved dosing regimens in patients with HAP, including VAP, current evidence indicates that maximal dosing regimens should be considered for treatment of pneumonia to achieve therapeutic concentrations at the site of infection.

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Competing Interests

Jason Roberts would like to declare collaborations with MSD, Bayer, Astellas, Pfizer, bioMerieux and Accelerate Diagnostics.

Ethical Approval

Not required

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijantimicag.2018.11.011.

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