Defining Antibiotic Dosing in Lung Infections

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Abstract: Defining optimal antibiotic dosing for treatment of lung infections is challenging because of the interrelationship between patient characteristics (eg, pathophysiological changes of lung during an infection, albumin level, renal function), antibiotic characteristics (eg, physicochemical properties, protein binding), and bacterial pathogen susceptibility. Measurement of antibiotic concentration in the lung compartments, such as epithelial lining fluid (ELF), is important to describe the drug exposure at site of infection. This article reviews published data on antibiotic penetration described by the ELF to plasma (ELF:plasma) ratios and the probability of pharmacokinetic/pharmacodynamics (PK/PD) attainment at the target site with current dosing regimens to outline dosing strategies that could optimize the PK/PD indices. Antibiotic physicochemical properties could be used to predict the extent of penetration into the lung tissues. Lipophilic antibiotics penetrate well into the lung compartments; however, standard dosing regimens generally seem to be insufficient to achieve optimal PK/PD indices in the ELF, particularly during severe infections. Aggressive dosing regimens are required for antibiotics that poorly or moderately penetrate the lung tissues, whereas nebulization could be the alternative method to enhance antibiotic concentration at the target site. Special populations such as the critically ill, patients on renal replacement therapy, and those with renal impairment need dosing to be individualized, as these populations have high PK variability. Dosing based on free drug concentrations should be considered preferred, as these concentrations frequently reflect the antibiotic concentration at the target site. Therefore, the use of therapeutic drug monitoring should be considered necessary, whenever possible, to guide dosing in lung infection.

Key Words: pharmacodynamics, pharmacokinetics, PK/PD, pulmonary, therapeutic drug monitoring

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Lung infection is common in hospitalized patients and is associated with considerable morbidity and mortality. This was comprehensively shown in a prevalence study of infection in the intensive care unit (ICU), where 64% of infections were respiratory infections in which these patients had higher ICU and hospital mortality rates.[1] Inadequate empirical antibiotic therapy is associated with reduced survival in patients with severe lung infection[2] and, thus early and appropriate antibiotic therapy is an essential intervention.[3] Optimizing antibiotic exposure for lung infections is challenging, especially when considering drug penetration into the lung tissue. Although infection can occur throughout most of the lung, alveolar compartments such as epithelial lining fluid (ELF) or the cells (alveolar macrophage, AM) are considered as the area where pathogens commonly accumulate during lung infections and thus antibiotic penetration into such compartments is of high importance.[4] Sufficient antibiotic concentrations in the ELF or AM are likely to enable optimal antibiotic activity at the site of infection in the lung. However, changes in the lung pathology in infected patients may reduce the likelihood of achieving target concentrations at the site of infection.

The decreasing susceptibility of respiratory pathogens further complicates this situation. On the basis of the European Committee on Antimicrobial Testing (EUCAST),[5] the minimum inhibitory concentration (MIC) breakpoint for the classical respiratory pathogen, *Streptococcus pneumoniae* reached 2 mg/L for the commonly used antibiotic, levofloxacin. Although in cases of nosocomial infection, MIC breakpoints for gram-negative pathogens, for example, *Pseudomonas aeruginosa* (16 mg/L for piperacillin/tazobactam), can be high and difficult to achieve in some patients.

The objective of this paper is to review and interpret the data describing antibiotic pharmacokinetics/pharmacodynamics (PK/PD) in critically ill patients with lung infections and to discuss target site penetration and the potential need for altered dosing strategies to increase the likelihood of successful treatment.

SEARCH STRATEGY AND SELECTION CRITERIA

A PubMed search using relevant keywords was undertaken to identify relevant recently published the English language articles. Journal articles referenced in the primary article identified, if appropriate, were also cited. Search terms included: "carbapenem," "cephalosporin," "penicillin," "fluoroquinolone," "aminoglycoside," "oxazolidinone," "macrolide," "ketolide," "colistin," "lung infection," "respiratory infection," "pneumonia," "epithelial lining fluid," "alveolar concentration," "intrapulmonary concentration," "pharmacokinetic," and "pharmacodynamic." To emphasize the antibiotic PK/PD data in the lung tissue, only articles with data on antibiotic concentrations in blood and ELF were included.

PK/PD INDICES RELATED TO ANTIBIOTIC EFFICACY AND RESISTANCE

Achieving PK/PD indices associated with maximal bacterial killing will increase the likelihood of treatment efficacy. PK/PD relates PK parameters to PD, which describe antibiotic activity at different concentrations.[6] Different PK/PD indices have been defined for different classes of antibiotics (Table 1). These relationships have been defined through in vitro and in vivo studies in animals and humans.[7–9] For optimal bactericidal activity in the lung, high penetration into the ELF,

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TABLE 1. The PK/PD Indices of Different Class of Antibiotics

Antibiotic-Killing Characteristics	Definition of PK/PD Indices	PK/PD Indices
Concentration dependent	Ratio of the peak antibiotic concentration (C_{max}) to the MIC of the pathogen (C_{max}/MIC)	C_{max}/MIC = 8-10 (aminoglycoside)
Time dependent	Percentage of time during dosing interval for which the free concentration remain above the MIC of the pathogen (%f $T_{>MIC}$)	40%-70% f $T_{>MIC}$ (β-lactams) 40%-80% f $T_{>MIC}$ (linezolid)
Concentration dependent with time dependent	Ratio of the area under the concentration-time curve during a 24 h period (AUC_{0-24}) to the MIC of the pathogen (AUC_{0-24}/MIC)	AUC_{0-24}/MIC > 125 (fluoroquinolone) AUC_{0-24}/MIC ≥ 400 (vancomycin) AUC_{0-24}/MIC > 50 (colistin)

%f $T_{>MIC}$ indicates percentage of time in which the free drug concentration is above the MIC of the pathogen; AUC_{0-24}, area under the concentration-time curve during a 24-hour period; C_{max}, maximum concentration; MIC, minimum inhibitory concentration; PK/PD, pharmacokinetic/pharmacodynamics.

which is defined by the ELF concentrations relative to plasma, is likely to be advantageous.

PATHOPHYSIOLOGY CHANGES IN LUNG INFECTIONS AND FACTORS INFLUENCING ANTIBIOTIC PENETRATION INTO ELF

Many factors could contribute to the pathogenesis of lung infections such as nasal colonization, oropharyngeal or gastric colonization, aspiration or colonization of the artificial airway. The invasion of pathogens into the lung parenchyma stimulates immune mechanisms of defense. As the process progresses, pathogens can reach the alveoli with host defenses quickly overwhelmed by the virulence of the microorganism and/or the inoculum size. The ELF is the fluid that fills the alveolar space. To reach the ELF, the antibiotic must be able to diffuse across the blood-alveolar barrier, in which it depends on its physicochemical characteristics (eg, lipophilicity, molecular weight, protein binding) and patient-specific characteristics (eg, tissue permeability, renal function).

Physicochemical Properties

Excellent penetration into the alveolar compartments is more common with lipophilic antibiotics (eg, fluoroquinolones, macrolides, oxazolidinones).[10] The ELF to plasma ratio (ratio of the area under the concentration time curve (AUC) of antibiotic for 1 dosing interval in ELF:plasma) of fluoroquinolones is reported to be >100% when administered by either the oral or intravenous (IV) route.[11–13] Numerous studies have reported the extensive penetration of fluoroquinolones into the lung tissue (eg, AM)[13,14] with concentrations that were higher than those in plasma and ELF. Similarly with tigecycline and oxazolidinones, the ELF to plasma penetration is also high.[15,16] Inversely for hydrophilic antibiotics (eg, aminoglycosides, glycopeptides), poorer penetration into the lung compartments has been reported in many studies. The aminoglycosides' ELF:plasma penetration ratio has been reported between 12% and 32% in critically ill patients with severe lung infection.[17,18] The ELF:plasma penetration ratio for vancomycin is reported to be approximately ~15% in a similar population.[19] These data support the importance of drug physicochemistry as 1 important determinant of drug penetration.

Protein Binding

The importance of the free, or unbound, drug exposure at the site of lung infection (ELF) has been advocated by many studies.[12,20–22] Measurement of unbound concentrations in the ELF is likely to best describe antibiotic activity, particularly for highly protein bound antibiotics. In a prospective PK study of 13 critically ill patients with ventilator-associated pneumonia (VAP) treated with teicoplanin (>85% protein binding), the median unbound teicoplanin concentrations in blood and ELF were similar,[21] which suggested that the unbound fraction of drug penetrated well into the lung tissue. Dose adjustment should be made in patients with low albumin concentrations, such as critically ill patients, and the unbound fraction in blood could guide dosing.

Tissue Permeability

Another important factor that might influence the penetration of antibiotic into the alveolar compartments is tissue permeability, although predicting permeability may be difficult. Lamer et al[19] reported that in critically ill patients treated with IV vancomycin, that significantly higher vancomycin penetration was seen in patients with higher albumin concentrations in the ELF, 25% versus 14% ($P < 0.02$). In this context, albumin movement from plasma into ELF was seen as an indicator of lung inflammation and that inflammation was associated with higher antibiotic concentrations in ELF.

RECENT PK STUDIES OF VARIOUS ANTIBIOTICS: ELF PENETRATION WITH PK/PD TARGET ATTAINMENT

Recent PK studies have showed variable antibiotic penetration into the lung tissue based on ELF:plasma ratios. Of interest is the question whether current antibiotic dosing regimens optimize PK/PD target attainment at the site of lung infection. Studies comparing the ELF concentrations and plasma concentrations have generally shown that lipophilic antibiotics have superior penetration into the lung tissue. Table 2 summarizes the recently published PK studies and data on ELF:plasma ratios and the probability of PK/PD target attainment in the ELF for different current dosing regimens of different antibiotic classes.

β-lactam

β-lactam penetration into the lung tissue is variable. Penicillins penetrate the lung tissue approximately 40% to 50%,[23,24] cephalosporins range from 30% to 100%,[26,37,38] and carbapenems about 30% to 40%.[27,28,39] Standard doses that achieve PK/PD targets in blood are unlikely to achieve the same targets in the presence of severe nosocomial

TABLE 2. Plasma and ELF Concentrations of Different Class of Antibiotics (Oral and IV)

Antibiotics	Dosage Regimen	Population [No. Patients (n)]	Sampling Time (h)†	Plasma Concentration (mg/L)‡	ELF Concentration (mg/L)‡	ELF:Plasma Ratio‡	Probability PD Target Attainment in ELF*
β-lactams							
Piperacillin (Boselli et al[23])	4.5 g 8 h	Critically ill patients, severe bacterial pneumonia (n = 10)	Steady state	24.0 ± 13.8	13.6 ± 9.40	0.57‖	Low
Piperacillin (Boselli et al[24])	4.5 g (LD), 13.5 g/d (CI)	Critically ill patients with VAP (n = 20)	Steady state	25.3 (23.1-32.6)§# 102.4 (97.4-112.6)§**	12.7 (6.7-18.0)§# 44.1 (33.4-48.3)§**	0.46	Medium (MIC < 8 mg/L)
Piperacillin (Boselli et al[24])	4.5 g (LD), 18 g/d (CI)	Critically ill patients with VAP (n = 20)	Steady state	38.9 (32.9-59.6)§# 135.3 (119.5-146.2)§**	19.1 (14.0-21.5)§# 54.9 (45.2-110.3)§**	0.43	Medium (MIC < 16 mg/L)
Ceftazidime (Boselli et al[25])	2 g (LD), 4 g/d (CI)	Critically ill patients (n = 15)	Steady state	39.6 ± 15.2	8.2 ± 4.8	0.21‖	Low (MIC > 2 mg/L)
Cefepime (Boselli et al[26])	2 g (LD), 4 g/d (CI)	Critically ill patients with severe nosocomial pneumonia (n = 20)	Steady state	13.5 ± 3.3	13.7 ± 3.0	1.04‖	Low (MIC > 4 mg/L)
Meropenem (Conte et al[27])	0.5 g 8 h × 4 doses	Healthy volunteers (n = 20)	1 2 3 5 8	10.9 ± 1.3 5.2 ± 1.6 2.4 ± 0.9 0.3 ± 0.4 0.0 ± 0.0	5.3 ± 2.5 2.7 ± 1.8 1.9 ± 0.9 0.7 ± 0.4 0.2 ± 0.1	0.49-0.80	Low
Meropenem (Conte et al[27])	1 g 8 h × 4 doses	Healthy volunteers (n = 20)	1 2 3 5 8	19.0 ± 7.6 7.5 ± 1.3 5.3 ± 1.5 2.0 ± 1.3 0.0 ± 0.0	7.7 ± 3.1 4.0 ± 1.1 1.7 ± 1.4 0.8 ± 0.4 0.0 ± 0.0	0.32-0.53	Low
Meropenem (Conte et al[27])	2 g 8 h × 4 doses	Healthy volunteers (n = 8)	1 3	60.9 ± 8.0 12.8 ± 2.7	2.9 ± 1.0 2.8 ± 1.5	0.1‖ 0.2‖	Low
Ertapenem (Boselli et al[28])	1 g 24 h	Critically ill patients with early-onset VAP (n = 15)	1 12 24	30.3 (27.1-37.8)§ 4.8 (3.9-6.4)§ 0.8 (0.5-1.2)§	9.4 (8.0-10.7)§ 2.0 (1.1-2.5)§ 0.3 (0.2-0.4)§	0.32 (0.28-0.46)§	Medium (MIC ≤ 4 mg/L)
Macrolides							
Azithromycin (Capitano et al[13])	500 mg first dose then 250 mg daily × 4 doses (oral)	Patients undergoing diagnostic bronchoscopy (n = 16)	4 8 12 24	0.1 ± 0.0 0.1 ± 0.0 0.1 ± 0.9 0.0 ± 0.0	0.6 ± 0.4 0.7 ± 0.4 0.9 ± 0.5 0.9 ± 0.7	6.4 13.2 12.6 31.3	Medium (MIC < 1 mg/L)
Azithromycin (Rodvold et al[29])	500 mg daily × 5 doses (IV)	Healthy volunteers (n = 12)	4 12 24	0.4 ± 0.1 0.3 ± 0.0 0.1 ± 0.0	1.7 ± 0.7 1.3 ± 0.5 2.9 ± 1.8	4.6 5.1 20.4	High
Fluoroquinolones							
Levofloxacin (Nicolau et al[14])	750 mg daily × 5 d (oral)	Acute exacerbation of chronic bronchitis (n = 18)	4 12 24	8.0 ± 2.5 5.8 ± 1.2 2.2 ± 1.2	7.5 ± 3.1 8.4 ± 6.0 1.2 ± 0.9	0.9‖ 0.5‖	Medium (MIC ≤ 1 mg/L)
Levofloxacin (Zhang et al[30])	500 mg single dose (oral)	Patients with lower respiratory tract infections (n = 40)	1.2 ± 0.1 4.1 ± 0.2 8.1 ± 0.1 12.1 ± 0.1 24.2 ± 0.1	3.3 ± 3.0 4.1 ± 1.9 2.1 ± 1.1 1.9 ± 0.6 0.9 ± 0.6	3.4 ± 3.7 2.4 ± 2.0 1.6 ± 1.5 1.0 ± 0.9 0.9 ± 0.7	0.8 ± 0.4 0.6 ± 0.5 0.7 ± 0.3 0.5 ± 0.6 1.0 ± 0.9	Low
Levofloxacin (Boselli et al[31])	500 mg daily × 2 d (IV)	Critically ill patients, severe CAP (n = 12)	1 24	12.6 (12.0-14.1)§ 3.0 (2.1-3.3)§	11.9 (8.7-13.7)§ 3.9 (2.1-5.7)§	1.3 ± 3.1 1.2 ± 3.6	Medium (MIC ≤ 1 mg/L)
Levofloxacin (Boselli et al[31])	500 mg 12 h × 2 d (IV)	Critically ill patients, severe CAP (n = 12)	1 12	19.7 (19.0-22.0)§ 7.7 (7.4-11.9)§	17.8 (16.2-23.5)§ 11.8 (10.3-16.7)§	1.3 ± 4.6 1.1 ± 4.0	High (MIC > 1 mg/L)
Glycopeptides							
Vancomycin (Lamer et al[19])	15 mg/kg (at least 5 d) (IV)	Critically ill, ventilated (n = 14)	24	24.0 ± 10.0	4.5 ± 2.3	0.2‖	Low
Vancomycin (Georges et al[32])	30 mg/kg daily (IV)	Critically ill, ventilated, MRSA pneumonia (n = 10)	24	16.3 ± 5.8	0.8 ± 1.1‖	0.0‖	Low

TABLE 2. (*continued*)

Antibiotics	Dosage Regimen	Population [No. Patients (n)]	Sampling Time (h)†	Plasma Concentration (mg/L)‡	ELF Concentration (mg/L)‡	ELF:Plasma Ratio‡	Probability PD Target Attainment in ELF*
Vancomycin (Lodise et al[33])	1000 mg 12 h × 9 doses (IV)	Healthy subjects (n = 10)	4 and 12	NA	NA	0.7 ± 0.7¶	Low (MIC > 1 mg/L)
Teicoplanin (Mimoz et al[21])	12 mg/kg 12 h × 2 d, then 12 mg/kg daily	Critically ill patient with VAP (n = 13)	18-24	3.7 (2.0-5.4)§	4.9 (2.0-11.8)§	1.3 (0.5-3.3)§	Low
Aminoglycosides							
Tobramycin (Boselli et al[17])	7-10 mg/kg daily × 2 doses	Critically ill patients with VAP (n = 12)	0.5	22.4 ± 5.9	2.7 ± 0.7	0.1 ± 0.0	Low
Gentamicin (Panidis et al[18])	240 mg daily × 1 dose	Critically ill patients with VAP (n = 24)	0.5 1 2 4 6	13.4 ± 0.9 8.8 ± 0.6 6.4 ± 0.5 4.7 ± 0.5 3.8 ± 0.6	NA 3.0 ± 0.4 4.2 ± 0.4 3.1 ± 0.4 2.7 ± 0.4	NA 0.3 ± 0.1 0.9 ± 0.1 1.1 ± 0.3 0.7 ± 0.2	Low
Oxazolidinones							
Linezolid (Boselli et al[16])	600 mg 12 h × 2 d (IV)	Critically ill patients with VAP (n = 16)	1 12	17.7 ± 4.0 2.4 ± 1.2	14.4 ± 5.6 2.6 ± 1.7	1.1 ± 0.3 1.0 ± 0.3	Medium (MIC < 4 mg/L)
Linezolid (Boselli et al[34])	600 mg (LD), then 1200 mg/d (CI) × 2 d	Critically ill patients with VAP (n = 12)	48	7.1 (6.1-9.8)§	6.9 (5.8-8.6)§	1.0 (0.8-1.1)§	Medium (MIC < 4 mg/L)
Others							
Colistin (Imberti et al[35])	2 mU 8 h (at least 2 d)	Critically ill patients with VAP (n = 13)	1 8	2.2 ± 1.1 1.0 ± 0.7	0.0	0.0	Low
Colistin (Markou et al[36])	225 mg 8 h (4-12 d)	Critically ill patients (n = 2)	1.5-4.0	3.3 ± 0.4‖	15.3 ± 14.8‖	4.6 ± 4.0‖	NA

*Susceptibility breakpoint based on EUCAST [5] and targeted PD indices [7–9] of at least 50% $fT_{>4xMIC}$ for β-lactam, $AUC_{0-24}/MIC > 25$ for macrolide, $AUC_{0-24}/MIC > 125$ for levofloxacin, $AUC_{0-24}/MIC \geq 400$ for glycopeptide, $C_{max}/MIC \geq 10$ for aminoglycoside, $AUC_{0-24}/MIC > 50$ for linezolid, and $AUC_{0-24}/MIC \geq 50$ for colistin, unless otherwise stated.

†Sampling time after the last dose.

‡Value expressed as mean ± SD unless specified otherwise.

§Value expressed as median (range).

‖Calculated value based on reported data.

¶Value based on AUC_{0-24} (mg h/L).

#Patients with no to mild renal impairment.

**Patients with moderate to advanced renal impairment.

CI indicates continuous infusion; ELF, epithelial lining fluid; H, hourly; IV, intravenous; LD, loading dose; MRSA, methicillin-resistant *Staphylococcus aureus*; NA, data not available; VAP, ventilator-associated pneumonia.

infection.[23–26] It follows that more aggressive dosing regimens may be required, especially in severe infections with more resistant pathogens. Continuous infusion (CI) could also be used as alternative administration for β-lactams in lung infections.[24–26,40,41] In patients with moderate to severe renal failure, a reduction in drug clearance may help in the achievement of PK/PD targets with usual dosing regimens.[24]

Macrolides

The macrolides penetrate well into the lung tissue (> 100% ELF:plasma ratio).[13,29,42] Previous studies have consistently reported significantly higher concentrations in ELF and AM than in plasma throughout the therapy course, with concentrations in AM always far higher than ELF. Rapid distribution of macrolides into the lung compartments had resulted in lower plasma concentrations throughout dosing interval,[13,29,42] thus leading to theoretical concerns of its use in primary bacteremia. In healthy adults administered standard doses of azithromycin, at the end of 24-hour dosing interval, 100% ELF concentrations (n = 4) were above the susceptibility breakpoint of 1 mg/L.[29] Although standard doses achieve desired concentrations in the lung tissue of healthy volunteers,[29,42] there are limited data available to evaluate the adequacy of these dosing regimens in infected patients.

Fluoroquinolones

Fluoroquinolones such as levofloxacin generally show excellent penetration into intrapulmonary sites.[14,30,31] Some studies have shown parallel relationships between plasma and ELF concentrations of levofloxacin after oral and IV administration.[30,31] Figure 1 is a PK model describing this relationship and suggests that at steady state, plasma PK could be used to guide dosing when the lung is the source of infection. Peak concentrations will be achieved in the ELF

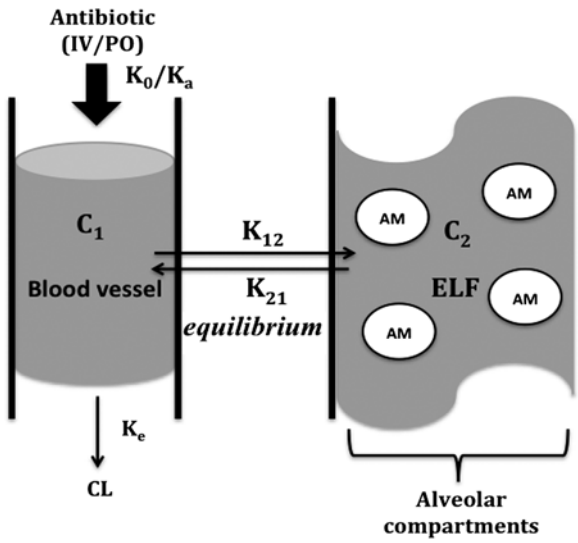

FIGURE 1. A pharmacokinetic description of drug distribution between blood and alveolar compartments. After drug administration (IV/PO), drug distributes from the blood compartment to the peripheral compartment (alveolar) (distribution phase). At steady state, the concentration of drug in blood (C_1) and alveolar (C_2) are equivalent. Drug is removed from the body through the elimination rate constant (K_e). Clearance (CL) = $K_e \times V_d$, where V_d is the apparent volume of distribution which is the sum of $V_1 + V_2$ (V_1 is volume of distribution in blood and V_2 is volume of distribution in alveolar compartments). AM indicates alveolar macrophage; ELF, epithelial lining fluid; IV, intravenous; K_o, rate constant after IV administration; K_a, absorption rate constant after oral administration; K_{12}, transfer rate constant from blood to alveolar compartments; K_{21}, transfer rate constant from alveolar compartments to blood; PO, by mouth.

approximately an hour after administration.[30,31] Standard doses of levofloxacin rarely achieved the desired PK/PD targets in infected younger patients and those without renal impairment.[12] In critically ill patients, the administration of a higher doses (eg, 1000 mg/d) achieve the targeted PK/PD index, $AUC_{0\text{-}24}/MIC > 125$ for levofloxacin in ELF.[31] Achieving these PK/PD targets is important with 1 study finding that when the PK/PD targets were achieved, >85% had microbiological and clinical cure. Importantly, dose adjustment should be considered necessary in renal dysfunction or in the elderly, as these patients will have a reduced clearance of levofloxacin.[12,13] With the excellent penetration into the lung tissue, use of fluoroquinolones in lung infections is usually reliable as long as pathogen susceptibility remains acceptable. Higher dosing regimens will be of course necessary when aiming for a more aggressive PK/PD targets.

Glycopeptides

Vancomycin was shown to penetrate well (~70%) in noninfected lung tissue[33] as compared with critically ill patients with pneumonia (<20%).[19,32] However, in healthy volunteers, standard dosing (1 g IV 12 h) rarely achieved the desired PK/PD target, $AUC_{0\text{-}24}/MIC$ ratio of ≥400 in the ELF (assuming an MIC 1 mg/L).[33] Thus with the poor lung penetration in infected patients, standard dosing would rarely achieve sufficient drug exposures in the ELF. Maintaining a constant plasma concentration (eg, 20 mg/L) to enhance drug concentrations in the lung compartment,[19,32] supports the use of therapeutic drug monitoring (TDM) to guide dosing with vancomycin.[43] The use of vancomycin to treat less susceptible pathogens in lung infection could be considered unreliable due to this low penetration and the need for higher doses to achieve the PK/PD target in the lung compartments, although clinical studies do not strongly reflect this at this time.[44]

Aminoglycosides

Similar to other hydrophilic antibiotics, aminoglycosides (eg, tobramycin, gentamicin, amikacin) are not considered to penetrate well into the pulmonary compartments. In critically ill patients with VAP,[17,18] standard dosing regimens failed to achieve the target PK/PD index, $C_{max}/MIC > 10$. As aminoglycosides poorly penetrate the lung tissue, higher doses may be required to treat severe lung infections. However, aiming for aggressive dosing with aminoglycosides may be impractical due to the potential toxicity associated with high doses.

Oxazolidinones

Linezolid had shown excellent penetration (>100%) into the pulmonary compartments in critically ill patients with VAP.[16,34] The administration of standard doses (eg, 1200 mg/d) commonly achieved PK/PD targets for pathogens with a susceptibility breakpoint of <4 mg/L in the ELF.[16] Furthermore, CI has been shown to be advantageous for achieving even higher PK/PD target attainment.[34] The measurement of unbound concentrations in the ELF for oxazolidinones may be necessary to guide for optimal dosing.

Others

Limited data are available to provide robust dosing for colistin during lung infections. Variable reports of colistin penetration into the lung tissue have been published. Imberti et al[35] reported an undetectable colistin concentration in BAL at steady state, after at least 2 days therapy of a lower dose (174 mg IV 8 h). However, in another study, the administration of a 30% higher dose of colistin (225 mg IV 8 h) in 2 mechanically ventilated trauma patients showed better ELF penetration, with a high ELF:plasma ratio of 5.[36] Despite the conflicting results, both of these reports agree that a higher dosing regimen is required to treat severe lung infections, particularly in critically ill patients.[35,36] The variation of penetration above is likely to be related to the nature of the lung injury, rather than other drug-related factors. It follows that consideration of inhaled colistin is warranted in these clinical scenarios.

ALTERNATIVE DOSING STRATEGIES: NEBULIZATION

Nebulization has been used for many years to deliver drugs into the lung compartments. In recent years, this method has also been extended for antibiotic treatment of lung infections. Nebulization aims to enhance the amount of antibiotic at the site of lung infection by delivering the drug at an anatomically closer location, which can also lead to reduced systemic exposure of drug. This mode of administration has been applied for hydrophilic antibiotics that have traditionally been considered to poorly penetrate the lung tissue. PK studies reporting antibiotic concentrations in the lung compartments using nebulization are becoming increasingly reported.[45,46] Athanassa et al[45] evaluated 20 critically ill patients with ventilator-associated tracheobronchitis treated with nebulized colistin. After the first nebulization, the median ELF concentrations were 6.7 and 2.0 mg/L at 1 and 8 hours, respectively. At these times, the median concentration in serum were 1.2 and 0.31 mg/L, respectively, indicating higher colistin

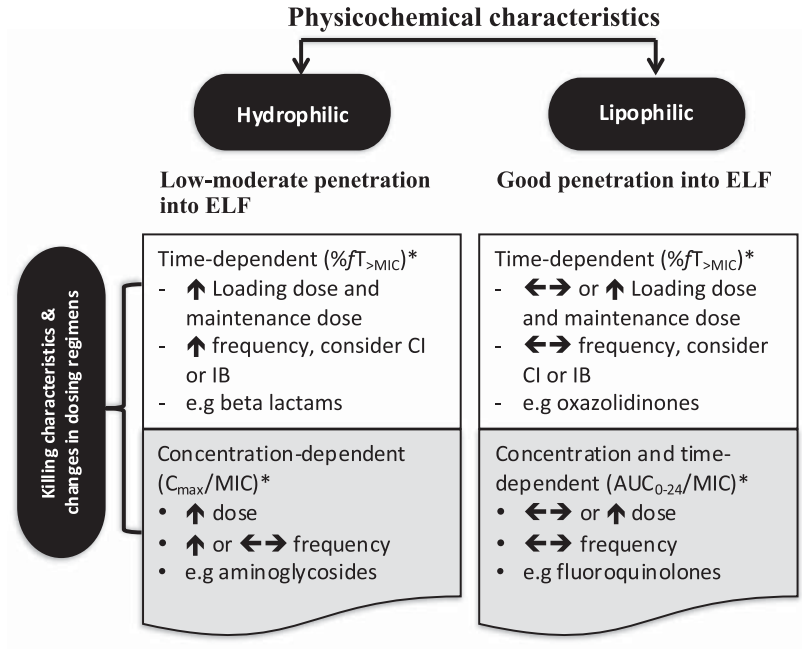

FIGURE 2. Antibiotic dosing strategies in lung infection.

concentrations can be achieved in the ELF with nebulization,[45] which suggests improved target site concentrations with nebulization. Luyt et al[46] similarly showed favorable amikacin concentrations in ELF in a study of 28 mechanically ventilated patients with gram-negative VAP. In this study, patients received nebulized amikacin through an advanced nebulizer system as an adjunct to IV therapy. The median peak amikacin concentration in the ELF (976 mg/L) was far higher than that observed in serum (0.85 mg/L).[46]

With the advancement of this antibiotic delivery system, nebulization may prove to be an effective alternative method of administration to improve antibiotic concentrations in the lung tissue. However, issues relating to appropriate dose selection in the context of pathogen susceptibility need to be considered.[45] Further, TDM to prevent any local or systemic unwanted effects[46] as well as use of a specially formulated antibiotic solutions for inhalation and delivery devices should be considered.[46]

RECOMMENDED DOSING APPROACH DURING LUNG INFECTION

The published data on the ELF:plasma ratios provide only a moderate level of understanding of antibiotic disposition in the lung. Evaluation of PK/PD target attainment in the ELF with current dosing regimens is required to define the optimal antibiotic dosing strategies for treatment of lung infections (Fig. 2).

Lipophilic antibiotics generally penetrate well into the lung tissue, and thus standard dosing will achieve the PK/PD targets for susceptible pathogens. Aggressive dosing may be necessary for treatment of less susceptible pathogens. Dosing for hydrophilic antibiotics is more challenging, particularly in critically ill patients. Standard dosing regimens rarely achieve the PK/PD targets in the lung tissue. The problem is likely to be heightened in patients with altered antibiotic clearance (CL) (eg, augmented renal clearance, renal replacement therapy)[47,48] and/or an increased volume of distribution (eg, critically ill patients, burns),[49,50] and therefore higher doses may be necessary in these populations. Use of nebulization to enhance drug delivery into the lung compartments is likely to be advantageous as well.

The bacterial kill characteristics of the different classes of antibiotics should be used to guide dosing. Aiming for a high C_{max}:MIC ratio using larger doses is especially important for antibiotic classes like the aminoglycosides. More frequent administration to maximize the percentage of time in which the free antibiotic concentration is above the MIC (%$fT_{>MIC}$) should be considered for time-dependent antibiotics like the β-lactams. Alternatively, use of extended infusion or CI should be considered as other approaches to increase $fT_{>MIC}$. Administration of intermittent doses can enable achievement of target AUC_{0-24}/MIC ratios for antibiotic classes such as the fluoroquinolones.

CONCLUSIONS

Antibiotic dosing for lung infections is challenging and understanding the relationship between the antibiotic and the pathophysiology changes in the lung during an infection is required. The alveolar compartments (ELF, AM) best represent the site of infection in the lung, and as such dose adjustment based on the antibiotic penetration into the ELF or AM may lead to the development of better antibiotic dosing regimens to treat lung infections. TDM should be utilized whenever possible as a mechanism to optimize dosing.

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