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Guideline

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Chinese consensus guidelines for therapeutic drug monitoring of polymyxin B, endorsed by the Infection and Chemotherapy Committee of the Shanghai Medical Association and the Therapeutic Drug Monitoring Committee of the Chinese Pharmacological Society

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Abstract: Polymyxin B, which is a last-line antibiotic for extensively drug-resistant Gram-negative bacterial infections, became available in China in Dec. 2017. As dose adjustments are based solely on clinical experience of risk toxicity, treatment failure, and emergence of resistance, there is an urgent clinical need to perform therapeutic drug monitoring (TDM) to optimize the use of polymyxin B. It is thus necessary to standardize operating procedures to ensure the accuracy of TDM and provide evidence for their rational use. We report a consensus on TDM guidelines for polymyxin B, as endorsed by the Infection and Chemotherapy Committee of the Shanghai Medical Association and the Therapeutic Drug Monitoring Committee of the Chinese Pharmacological Society. The consensus panel was composed of clinicians, pharmacists, and microbiologists from different provinces in China and Australia who made recommendations regarding target concentrations, sample collection, reporting, and explanation of TDM results. The guidelines provide the first-ever consensus on conducting TDM of polymyxin B, and are intended to guide optimal clinical use.

Key words: Polymyxin B; Therapeutic drug monitoring (TDM); Pharmacokinetics; Clinical efficacy

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1 Introduction

Increasing multidrug-resistant and extensively drug-resistant Gram-negative bacteria in clinics now pose a great therapeutic challenge worldwide. Data from the Chinese Antimicrobial Surveillance Network (CHINET; https://www.chinets.com) show that carbapenem-resistant *Acinetobacter baumannii* (CRAB) and *Klebsiella pneumoniae* (CRKP) increased from 32.9% and 3.0% in 2005 to 66.5% and 21.9% in 2021, respectively. However, new antibacterial drug development is slow (Theuretzbacher et al., 2019; Behzadi et al., 2021) and available clinical treatment options for carbapenem-resistant organisms are extremely limited. Polymyxin antibiotics were approved in the late 1950s but were subsequently replaced by "less toxic" antibiotics. However, they retain substantial activity against many problematic Gram-negative pathogens (Gales et al., 2012; Jones et al., 2013) and have since appeared in clinics again to treat these difficult infections. The currently available parenterally administered polymyxins are polymyxin B (sulphate) and colistin; the latter is available as both colistin sulphate (in China) and the inactive prodrug colistimethate (sodium) (Li et al., 2006; Cai et al., 2015; Nang et al., 2021). Although antibiotics such as ceftazidime/avibactam have recently become available, polymyxins are still considered last-line antibiotics for treatment of CRKP (e.g., New Delhi metallo-β-lactamase), as well as the multidrug-resistant *A. baumannii* (MDRAB) and *Pseudomonas aeruginosa* (MDRPA) (CDC, 2019).

Optimizing parenteral polymyxin therapy is challenging. Of great concern is that resistance to the polymyxins is emerging, with low polymyxin exposure a contributing factor (Hermes et al., 2013). Unfortunately, simple dose escalation is precluded due to nephrotoxicity, which occurs in up to 60% of patients receiving intravenous administration (Azad et al., 2019; Pogue and Tam, 2019). Therefore, therapeutic drug monitoring (TDM) of polymyxins is recommended to reduce both the emergence of resistance and adverse reactions, especially nephrotoxicity. TDM requires multidisciplinary cooperation between clinicians, nurses, testing technicians, and clinical pharmacists for dose optimization. It is necessary to standardize polymyxin TDM operating procedures and analyze the influential factors during the TDM process to ensure that it is conducted accurately and to provide evidence for the rationality of the operating procedures. Although both polymyxin B and colistin (the latter usually administered as colistimethate) are currently available in China for intravenous administration, the requirements for TDM are specific to each antibiotic. This is due in part to the different patient populations/indications for which they are generally recommended with colistimethate being advantageous in the treatment of urinary tract infections (where high colistin concentrations are achieved in urine due to active excretion of colistimethate by the kidneys) and polymyxin B being superior for treatment of serious systemic infections in critically ill patients (administered as an active component). They also have different chemical properties which necessitate different conditions for storage of TDM samples and transfer to testing laboratories (colistimethate is unstable and converted to colistin at room temperature), as well as different liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods for detection of the active entity. Given these differences and the greater use of polymyxin B in China due to its pharmacokinetic advantages over colistimethate (which requires in vivo conversion to colistin), the TDM consensus guidelines in the present paper will focus on polymyxin B.

This consensus is specified for the TDM of polymyxin B, and covers the whole process of conducting TDM (including the necessity; target patient population; the explanations and technical notes for target concentrations, sample collection, concentration measurements, and reporting; explanation of TDM results and dose adjustment; as well as quality control and quality assurance). The purpose of the consensus is to provide practical and operational guidelines to professionals such as physicians, clinical pharmacists, and testing laboratorians, for conducting TDM and precision dosing of polymyxin B.

2 Methods

This consensus was initiated by the Infection and Chemotherapy Committee of the Shanghai Medical Association and the Therapeutic Drug Monitoring Committee of the Chinese Pharmacological Society. The consensus panel was composed of two clinicians, 21 pharmacists, and one microbiologist from ten provinces in China and Australia. Relevant professional

issues were discussed in meetings, arising from a review of English and Chinese literature (conducted before May 10, 2022). The recommendations were developed based on the most up-to-date evidence from Chinese and international sources and were designed to meet existing clinical needs. The consensus was externally reviewed by independent experts: three clinicians, 17 pharmacists, and two microbiologists from 12 provinces in China. The external experts individually graded the strength of each recommendation as either strong, medium, weak, or not supported. The definitions for the recommendation grading are listed in Table 1. For each recommendation, the level chosen by the external experts is reported as the percentage of experts choosing each level. The expert group reviewed the external review results and revised recommendations where necessary to reach a final consensus.

3 Necessity for polymyxin B TDM

Polymyxin B is used as a "last-line" antibiotic for patients with severe systemic infection caused by extensively drug-resistant bacteria (CDC, 2019). Polymyxin B exhibits concentration-dependent bacterial killing (Li et al., 2001; Tam et al., 2005; Bulitta et al., 2010; Bergen et al., 2011a, 2011b; Landersdorfer et al., 2018). The pharmacokinetic/pharmacodynamic (PK/PD) index most closely associated with polymyxin antimicrobial activity is the *f*AUC/MIC (the area under the unbound drug concentration curve to the minimum inhibitory concentrations (MICs)) (Bergen et al., 2010; Dudhani et al., 2010a, 2010b; Deris et al., 2012; Cheah et al., 2015; Landersdorfer et al., 2018). Intravenously administered polymyxin B has a narrow therapeutic window and dose-limiting nephrotoxicity. The frequent necessity for simultaneous use of various other drugs such as calcineurin inhibitors, acute loop diuretics, and vasopressors further increases the risk of nephrotoxicity (Naesens et al., 2009; Gul et al., 2016; Ciftci et al., 2018). The incidence of nephrotoxicity of intravenous polymyxin B globally is 20%–60% (Javan et al., 2015; Zavascki and Nation, 2017; Azad et al., 2019; Pogue and Tam, 2019; Wang et al., 2021). In Chinese patients over the last three years, the incidence of acute kidney injury (AKI) following intravenous administration of polymyxin B ranged from 21.7% to 32.9% in prospective studies (Wang et al., 2021; Zhang et al., 2021) and 19.0% to 38.7% in retrospective studies (Jia et al., 2022; Wen et al., 2022). Risk factors for AKI include age, weight, chronic comorbidities, septic shock, hypoalbuminemia, and concomitant use of nephrotoxic drugs (Phe et al., 2014; Deng et al., 2021). Although polymyxin B dose reduction reduces the risk of nephrotoxicity, it increases the likelihood of treatment failure and emergence of polymyxin resistance (Hermes et al., 2013; Olaitan et al., 2014). Moreover, the physiological and pathological changes in critically ill patients affect the pharmacokinetics of polymyxin B. Therefore, it is difficult to adjust the dosage regimen to achieve rapid attainment of effective polymyxin B concentrations; and dose adjustment based solely on clinical experience creates a risk of toxicity, treatment failure, and the emergence of resistance. There is thus an urgent clinical need to perform TDM of polymyxin B to optimize the use of this "last-line" therapy.

4 Recommendation of polymyxin B TDM in patient populations

It is recommended that critically ill patients, burn patients, neonates/children, the elderly (65 years or older), overweight or obese patients (body mass index (BMI)$\geqslant$ 25 kg/m^2), underweight patients (BMI$\leqslant$18.5 kg/m^2), those with an elevated risk of nephrotoxicity (such as those receiving concomitant treatment with other nephrotoxic drugs) or with augmented renal clearance, and those receiving renal replacement therapy or who are on a long course of treatment (>5 d) all receive polymyxin B TDM (Wong et al., 2014; Lanckohr et al., 2021).

Table 1 Grading definitions for strength of recommendations

Strength category	Definition
Strong	Strong evidence, and the external panel member agrees that the recommendation is beneficial for patients.
Medium	Less evidence, and the external panel member agrees that the recommendation is beneficial for patients.
Weak	Less evidence, and the external panel member considers that the recommendation is less beneficial for patients.
Not supported	No evidence, and the external panel member considers that the recommendation is not beneficial for patients.

5 Target concentrations, sample collection, concentration measurement, and reporting for polymyxin B TDM

5.1 TDM target for polymyxin B

Based on PK/PD studies undertaken in mouse thigh infection models employing *A. baumannii*, *P. aeruginosa*, and *K. pneumoniae* and in human patients (Sandri et al., 2013; Cheah et al., 2015; Kubin et al., 2018; Landersdorfer et al., 2018; Miglis et al., 2018; Liu et al., 2021), an area under the total plasma concentration-time curve across 24 h ($AUC_{24\,h}$) of 50 mg·h/L was identified for colistin and polymyxin B as the lower limit for effective treatment of pathogens with MICs of ⩽2 mg/L. Using data from 17 studies that examined the nephrotoxicity of intravenous polymyxin B and original Monte Carlo simulations, Lakota et al. (2018) identified that an area under the plasma concentration-time curve across 24 h at steady state ($AUC_{ss,\,24\,h}$) of 100 mg·h/L resulted in mild nephrotoxicity, and ultimately proposed a target $AUC_{ss,\,24\,h}$ window of 50–100 mg·h/L for polymyxin B, for pathogens with MICs of ⩽2 mg/L. Wang et al. (2021) compared the population pharmacokinetic properties of polymyxin B in Chinese patients and concluded that the $AUC_{ss,\,24\,h}$ was significantly higher in patients that experienced AKI ((108±70) mg·h/L) compared to those without AKI ((66±34) mg·h/L). The 2019 International Consensus Guidelines for the Optimal Use of Polymyxins recommended that for polymyxin B the $AUC_{ss,\,24\,h}$ should be about 50 mg·h/L and possibly 50–100 mg·h/L, with the latter corresponding to an average steady-state concentration across 24 h ($C_{ss,\,avg}$) of 2–4 mg/L (Tsuji et al., 2019). The Chinese Consensus Guidelines proposed here specify a PK/PD therapeutic window of 50–100 mg·h/L when making recommendations for clinical practice.

Recommendation 1: The recommended TDM target of polymyxin B-treated systemic infections for clinical efficacy and safety is a $C_{ss,\,avg}$ of 2–4 mg/L, corresponding to an $AUC_{ss,\,24\,h}$ of 50–100 mg·h/L.

Recommendation level as graded by external experts: strong (72.7%); medium (27.3%); weak (0%); not recommended (0%).

5.2 Recommended sampling time

For patients with severe infections, the International Consensus Guidelines for the Optimal Use of Polymyxins recommend a polymyxin B loading dose of 2.0–2.5 mg/kg total body weight (TBW) infused over 1 h, with subsequent 12-h maintenance doses of 1.25–1.50 mg/kg TBW infused over 1 h (1 mg is equivalent to 10 000 international units (IU) (Tsuji et al., 2019). The peak concentration (C_{max}) and trough concentration (C_{trough}) are achieved at the end of the first infusion and immediately before the next infusion at steady state, respectively (Liu et al., 2021). An approach requiring two samples is commonly applied in TDM, with the AUC calculated using a first-order elimination method (Rybak et al., 2020).

Recommendation 2: For patients with normal renal function and in the absence of a loading dose, TDM samples should be collected before and after the fourth or fifth dose. If a loading dose is administered, samples can instead be collected before and after the second or third dose. Samples for trough concentrations should be collected no earlier than 0.5 h before the next infusion, and samples for peak concentrations should be collected within 0.5 h of the end of the infusion.

Recommendation level as graded by external experts: strong (68.2%); medium (31.8%); weak (0%); not recommended (0%).

Given the importance of early treatment, the target polymyxin B exposure should be achieved early in treatment (within the first 24–48 h). If a model-informed precision dosing (MIPD) and Bayesian estimation method is used to assist in individualized polymyxin B dosing, earlier concentrations before steady state can be collected to guide dose adjustment. In addition, MIPD offers opportunities for flexible sampling time during treatment (Wich et al., 2021). If dose adjustment is required after initial TDM, it is recommended to wait for two to three doses following the adjustment before TDM is repeated. As the time required to reach steady state may be longer in patients with renal insufficiency, attainment of steady state can be confirmed by performing additional trough sampling (with similar trough concentrations confirming steady state). For patients on long courses of treatment, hemodynamically unstable patients, or patients receiving renal replacement therapy, TDM could be conducted weekly to monitor whether dose adjustment is necessary.

5.3 Sample-collection tubes and transportation to laboratories

Sample-collection requirements are necessarily related to the analysis method. Prior communication

with the testing laboratory is essential to ensure the appropriate choice of specimen-collection tube and collection of an adequate volume of blood.

In whole blood, polymyxin B is stable in ethylenediaminetetraacetic acid (EDTA) or heparin tubes for at least 10 h at room temperature and for at least 19 h at (2−6) ℃ (Deng et al., 2021). In plasma, it is stable in EDTA or heparin tubes for at least 22 h at room temperature and at least 24 h in EDTA anticoagulant plasma when refrigerated at 2–8 ℃ (Liu et al., 2020). Polymyxin B samples in EDTA anticoagulant plasma are stable for at least 141 d at −20 or −70 ℃ and can be freeze-thawed at least three times (Liu et al., 2020). Accordingly, data from the literature would suggest that blood samples containing polymyxin B (with EDTA or heparin as the anticoagulant) need to be transferred to testing laboratories at room temperature within 10 h of collection when stored at room temperature (25±5) ℃ and within 19 h of collection when stored on ice. Importantly, as the stability of the sample is dependent upon the storage tube, temperature, and composition (whole blood or plasma), the testing laboratory is still required to investigate the stability of TDM samples and provide information to clinicians and nurses for appropriate collection and transfer of samples (Chinese Pharmacopoeia Commission, 2020).

5.4 Analysis methods

5.4.1 Analytes

Analysis methods for polymyxin B include microbiological, high-performance liquid chromatography (HPLC), LC-MS/MS, and immunoassay methods, each of which has different sensitivity and suitability (Sun et al., 2009; Thomas et al., 2012; Wang et al., 2017; Burkin et al., 2021). The most suitable method for the TDM requirements of polymyxin B is LC-MS/MS. It is important to recognize that polymyxin B sulfate is a fermented mixture produced by *Paenibacillus polymyxa* (previously known as *Bacillus polymyxa*) that consists of more than 30 components, the two main components in commercial preparations being polymyxins B1 and B2 (which constitute more than 80% of the total polymyxin B) (Zavascki et al., 2008; Wang et al., 2017; Liu et al., 2020; Tam et al., 2020; Deng et al., 2021). Previously published LC-MS/MS methods have focused on determining the concentrations of these two major components (Liu et al., 2020; Wang et al., 2020; Deng et al., 2021). An in-house LC-MS/MS method developed for the detection of polymyxin B can be used for TDM once validated according to the Expert Consensus on Quality Assurance of Chromatographic Technology for Therapeutic Drug Monitoring (2021 Edition) (Division of Therapeutic Drug Monitoring, Chinese Pharmacological Society et al., 2021) and the 9012 Guidelines for Validation of Quantitative Analysis Methods of Biological Samples (Chinese Pharmacopoeia Commission, 2020).

After determination of the concentrations of polymyxins B1 and B2 via LC-MS/MS, the concentration of polymyxin B is calculated and reported in the TDM report. The calculation is based on the molar concentration of polymyxin B and its components according to the following Eq. (1):

$$C_B = (C_{B1}/\mathrm{Mol}_{B1} + C_{B2}/\mathrm{Mol}_{B2}) \times \mathrm{Mol}_{avgB}, \quad (1)$$

where C_B is the total polymyxin B concentration; C_{B1} and C_{B2} are the concentrations of polymyxins B1 and B2, respectively; Mol_{B1} and Mol_{B2} are the molar weights of polymyxins B1 (1203.48 g/mol) and B2 (1189.45 g/mol), respectively; and Mol_{avgB} is the average molar weight of polymyxin B, calculated based on the amounts of polymyxins B1 and B2 in each batch.

It should be noted that this calculation underestimates the polymyxin B concentration by about 15%–20% given that polymyxins B1 and B2 comprise only about 80%–85% of total polymyxin B.

5.4.2 Analyte reference standard

It is essential to use qualified standard analytes for quantitative analysis. Due to access or price-limitation issues in obtaining pure standards of polymyxins B1 and B2, mixtures of polymyxin B standard with detailed composition and purity information are alternative choices. If only the polymyxin B sulfate content is indicated in the standard certificate of analysis (COA), concentrations of polymyxin B base should be employed, not the sulphate form.

5.4.3 Self-developed LC-MS/MS method notes

Because polymyxins are complex mixtures with similar structures, developing an analysis method is challenging. First, precursor ions with two or three charges are observed in LC-MS/MS for polymyxins B1 and B2. As the intensity responses of polymyxins B1 and B2 with three charges are different from the

responses of those with two charges, it is necessary to monitor suitable ion pairs according to the sensitivity of the instrument (Covelli et al., 2017; Liu et al., 2020). Second, the high cost of an isotopic internal standard of a single component of synthetic polymyxin B means that structural analogs of polymyxin B, or pure polymyxin E1 or polymyxin E2, are often used as internal standards in reported methods (Covelli et al., 2017). However, it should be noted that if a patient is concurrently receiving either colistin sulfate (also known as polymyxin E) or colistimethate—which would generally be administered via nebulization when given concurrently with intravenous polymyxin B—polymyxin E1 or E2 cannot be used as an internal standard and another polymyxin (e.g., polymyxin D1) should be used. Finally, the following must be avoided: adsorption of polymyxin B onto glass tubes or plastic products (Meng et al., 2016); interference (or cross-talk) in ion transitions between polymyxins B1, B2, or the internal standard in LC-MS/MS (Song, 2011; Covelli et al., 2017); and carryover from high-concentration (e.g., 10 mg/L) to low-concentration (e.g., 0.05 mg/L) samples. Notably, blood samples from patients with baseline diseases and complex concomitants may bring unexpected matrix effects that require attention during analysis (Furey et al., 2013; Panuwet et al., 2016). When matrix effects are observed, the method needs to be re-evaluated and measures need to be taken to minimize these effects, such as optimizing the sample preparation process, optimizing the chromatograph conditions, or applying an isotopic internal standard.

5.5 Calculation of $AUC_{ss,\,24\,h}$ and $C_{ss,\,avg}$

After determination of polymyxin B concentrations in blood samples, the TDM target ($AUC_{ss,\,24\,h}$ or $C_{ss,\,avg}$) can be calculated in either of the following two ways.

(1) First-order elimination-based equation method

Once the steady-state polymyxin B concentrations immediately before (C_{trough}) and after (C_{max}) infusion have been received from the testing laboratory, the infusion time ($t_{infusion}$) and dosing interval (τ) can be used to calculate the elimination constant (k_e) using the following Eq. (2) (Begg et al., 1995; Pai et al., 2014):

$$k_e = \frac{\ln C_{max} - \ln C_{trough}}{\tau - t_{infusion}}. \tag{2}$$

The $AUC_{ss,\,24\,h}$ is then calculated using either Eq. (3) or Eqs. (4) and (5) below (Pai et al., 2014):

$$AUC_{ss,\,24\,h} = \left[\frac{t_{infusion} \times \left(C_{max} + C_{trough}\right)}{2} + \frac{C_{max} - C_{trough}}{k_e}\right] \times n, \tag{3}$$

$$C_{soi'} = \frac{C_{max}}{e^{-k_e \times t_{infusion}}}, \tag{4}$$

$$AUC_{ss,\,24\,h} = \frac{C_{soi'} - C_{trough}}{k_e} \times n, \tag{5}$$

where C_{max} is the maximum concentration after administration; C_{trough} is the minimum (trough) concentration prior to the next dose; n is the number of doses in 24 h; $C_{soi'}$ is the exploration concentration at the commencement of dosing according to the one-compartmental linear elimination pharmacokinetics hypothesis. It should be noted that $AUC_{ss,\,24\,h}$ estimations based on Eq. (3) underestimate the $AUC_{ss,\,24\,h}$, while estimations based on Eqs. (4) and (5) overestimate the $AUC_{ss,\,24\,h}$. The $C_{ss,\,avg}$ can then be calculated using Eq. (6):

$$C_{ss,\,avg} = \frac{AUC_{ss,\,24\,h}}{24}, \tag{6}$$

where $C_{ss,\,avg}$ is the average concentration across 24 h at steady state.

(2) Population pharmacokinetics (popPK) model and Bayesian prediction method

Bayesian posterior algorithms with a well-developed popPK model have been widely used for vancomycin, especially since the development of drug dosing software (Rybak et al., 2020). An important advantage of popPK models and Bayesian prediction is that TDM samples can be collected at any time following drug administration. PopPK models for intravenously administered polymyxin B have been developed for a variety of patient groups including critically ill adult patients, cystic fibrosis patients, and patients whose infections are caused by MDR Gram-negative bacteria. These models applied one- and two-compartmental models with first-order linear elimination (Sandri et al., 2013; Avedissian et al., 2018; Manchandani et al., 2018; Miglis et al., 2018; Wang et al., 2021, 2022). The most common covariates were creatinine clearance (CrCL) and body weight. PopPK models can be used in conjunction with Bayesian feedback to predict

individual pharmacokinetic parameters and calculate $C_{ss,avg}$ or $AUC_{ss,24\,h}$ (Lunn et al., 2002; de Velde et al., 2018). Use of these published popPK models for TDM of polymyxin B needs to be carefully evaluated for both suitability of the patient population and accuracy of the model prediction. While studies that have summarized and evaluated previously published popPK models for polymyxin B have shown that bootstrap or visual predictive checks (VPCs) were satisfactory, external validation showed poor correlation between predicted and observed exposure (Chen et al., 2021, 2022; Li et al., 2021). The poor predictive value of these models may be due to many uncertainty factors, including the limited sample sizes during model development and external validation, cross-study discrepancy, variation in patient characteristics, and bioassay errors, as well as a lack of understanding of polymyxin B metabolic pathways in vivo. Pooled population pharmacokinetic analyses, large sample sizes, and multi-center prospective clinical studies for popPK or TDM (with central laboratory bioassay analysis) are requisite to resolve the issue.

Recommendation 3: Employ the first-order elimination-based equation method to calculate $AUC_{ss,24\,h}$ or $C_{ss,avg}$ when a suitable popPK model is not available.

Recommendation level as graded by external experts: strong (45.4%); medium (50.0%); weak (4.6%); not recommended (0%).

Recommendation 4: Apply a popPK model and Bayesian feedback to calculate $AUC_{ss,24\,h}$ or $C_{ss,avg}$.

Recommendation level as graded by external experts: strong (54.5%); medium (45.5%); weak (0%); not recommended (0%).

5.6 Biosafety

Transport of TDM samples from bedside to testing laboratory must be undertaken in accordance with biosafety requirements, including the use of biosafety transport boxes to prevent samples from being damaged and/or contaminated during transportation (Bielecka, 2018). If the samples are found to be damaged upon arrival at the testing laboratory, the clinical department should be immediately contacted and the samples should be rejected and disposed of correctly. Laboratory personnel also need to be protected from biological hazards in accordance with laboratory safety management regulations during sample processing and testing.

6 Explanation of TDM results and dose adjustment

6.1 Dose adjustment based on TDM target

TDM reports must include a variety of information including basic patient demographics, the name of the clinical department or unit that requested TDM, the type of tubes (anticoagulant or coagulant) in which the samples were collected, sample-collection time and the time received by the testing laboratory, the serial number or barcode of the samples, the drugs for which TDM was undertaken, testing equipment and methods, test results, and target ranges or reference values. The lower limit of quantification (LLOQ) will be dependent on the self-developed LC-MS/MS method and will differ between laboratories. Concentrations lower than the LLOQ should be reported as "<lower limit of quantification" (Duggan, 2019); concentrations higher than the upper limit of quantification should be reported either as ">upper limit of quantification" or alternatively remeasured following appropriate dilution. It is necessary to double-check the consistency between the raw data and the reported tested results with the information listed on the TDM report. It may be necessary to explain abnormal situations. It is recommended that qualified clinical pharmacists make individualized dosing recommendations based on TDM reports and the specific physiological and disease conditions of patients.

Recommendation 5: For patients with $C_{ss,avg}$< 2 mg/L or $AUC_{ss,24\,h}$<50 mg·h/L, dose adjustments should be based on clinical and microbiological efficacy. A dosage increase is recommended when the clinical condition of the patient is not improved.

Recommendation level as graded by external experts: strong (59.1%); medium (40.9%); weak (0%); not recommended (0%).

Recommendation 6: For patients with $C_{ss,avg}$> 4 mg/L or $AUC_{ss,24\,h}$>100 mg·h/L, the dose should be reduced based on TDM results in order to reduce the likelihood of nephrotoxicity.

Recommendation level as graded by external experts: strong (68.2%); medium (22.7%); weak (9.1%); not recommended (0%).

Due to the potential of nephrotoxicity, dose increases should be considered with much more caution in clinical settings. If good clinical and microbiology efficacy is achieved, then increasing the dose is not

necessary even when TDM results were shown lower than the target. However, if the TDM showed results higher than the target, the dose needs to be reduced, even when clinical efficacy is not improved. Other strategies such as synergistic combinations could be considered to improve efficacy.

The PK/PD index of polymyxin B is *f*AUC/MIC, so changing the single dose is more commonly recommended than changing the frequency of administration. Dose adjustment can be undertaken in either of the following two ways.

(1) Adjustments can be made using an equation-based method, for example by use of Eq. (7) (Begg et al., 1995):

$$\mathrm{Dose}_2 = \frac{\mathrm{AUC}_{\mathrm{targeted}}}{\mathrm{AUC}_{\mathrm{observed}}} \times \mathrm{Dose}_1, \tag{7}$$

where Dose_2 is the target adjustment dose; $\mathrm{AUC}_{\mathrm{targeted}}$ is the targeted area under the plasma concentration-time curve; $\mathrm{AUC}_{\mathrm{observed}}$ is the calculated area under the plasma concentration-time curve based on TDM; and Dose_1 is the initial maintenance dose.

(2) Alternatively, adjustments can be made based on a popPK model and dosing predictions with Bayesian predictions (Roberts et al., 2011).

6.2 Dose adjustment based on PK/PD

When individualized medication recommendations are made based on PK/PD calculations, it is important to consider the MIC of the infecting pathogen(s). Dose adjustment is based on a probability of target attainment (PTA) of ≥90%. PTAs are calculated through Monte Carlo simulations of the PK/PD index (*f*AUC/MIC) that are equal to or greater than the PK/PD targets for different pathogens, such as *A. baumannii*, *P. aeruginosa*, or *K. pneumoniae*. Notably, the MIC measurements are influential elements for PTA calculations and the accuracy of MIC results is important for dose adjustment. The recommended method for determining susceptibility to polymyxin B (i.e., MIC determination) is broth microdilution rather than agar dilution (Pogue et al., 2020). If a different susceptibility-testing method is used, the results generated need to be compared with those from broth microdilution and validated accordingly. Only MIC results from suitably validated methods should be accepted. In addition, it should be noted that even if broth microdilution is used for MIC determination, this method has a margin of error of ±1 dilution. Hence, when calculating PK/PD targets, errors in MIC determination should be considered and clinical responses should be monitored when making dose adjustments (Fratoni et al., 2021).

7 Quality control and assurance

Quality control and assurance measures for TDM of polymyxin B need to take into consideration the TDM management system, analysis methods, and clinical intervention related to TDM. The management system requires procedures for the implementation of TDM including personnel management, relevant technical documents, standard operating practices, and clinical intervention guidelines to ensure the progress of TDM. The cooperation of clinicians, nurses, laboratory analysts, and clinical pharmacists is required to ensure that all TDM processes such as dosing records, sampling, inspection, testing, and reporting are correctly followed and double-checked, and can be traced back for further investigation and clarification when necessary.

For testing laboratories, it is necessary to regularly calibrate the relevant testing equipment and offer appropriate training and assessment to the analysts. Daily intra- and inter-laboratory quality controls are needed to avoid random or systematic errors during analysis. When assessing the intra-laboratory quality control of polymyxin B, it is important to follow the requirements laid out in quality-control charts or in the 9012 Guidelines for Validation of Quantitative Analysis Methods for Biological Samples (Chinese Pharmacopoeia Commission, 2020). At least two quality-control samples at each of three concentrations (low, medium, and high) should be incorporated into daily analysis. In exceptional circumstances such as instrument failure or quality-control deviation, it is important to analyze the potential causes and take appropriate measures such as re-injection, re-assignment of quality control, or re-calibration.

Inter-laboratory comparison of polymyxin B should be carried out to avoid systematic errors affecting clinical practice. For other quality-assurance concerns, the Expert Consensus on the Standards of Therapeutic Drug Monitoring (2019 Edition) (Division of

Therapeutic Drug Monitoring, Chinese Pharmacological Society, 2019), the Expert Consensus on the Interpretation of Therapeutic Drug Monitoring (Division of Therapeutic Drug Monitoring, Chinese Pharmacological Society et al., 2020), and the Expert Consensus on Quality Assurance of Chromatographic Technology for Therapeutic Drug Monitoring (2021 Edition) (Division of Therapeutic Drug Monitoring, Chinese Pharmacological Society et al., 2021) should be consulted.

Terminology

$AUC_{ss, 24\ h}$: an area under the total plasma concentration-time curve across 24 h at steady state, which reflects in vivo drug exposure after administration of multiple doses of a certain drug.

Concentration-dependent killing: antibacterial activity correlated with peak concentrations or exposure to a drug.

Monte Carlo simulations: a mathematical method for estimating the possibility of likely outcomes of an event based on a range of input values, which is applied to pharmacokinetic/pharmacodynamic (PK/PD) simulations to calculate the probability of PK/PD target attainment and to assess antibacterial dosing regimens.

MIC (minimum inhibitory concentration): the lowest concentration of antibacterial agents able to inhibit the visible growth of bacteria in vitro.

popPK (population pharmacokinetics): an approach to studying the variabilities in drug concentrations within a patient population receiving a certain drug in clinics.

TDM (therapeutic drug monitoring): an important approach to individualized or precision dosing through maintaining plasma or blood drug concentration within the therapeutic window of a certain drug, which has become a multidisciplinary collaborative project among testing laboratorians, clinical pharmacists, and physicians, with the aim of optimal dosing.

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Author contributions

Xiaofen LIU, Chenrong HUANG, and Phillip J. BERGEN wrote and edited the manuscript. Liyan MIAO and Jing ZHANG initiated the consensus. Jian LI, Jingjing ZHANG, Yijian CHEN, Yongchuan CHEN, Beining GUO, Fupin HU, Jinfang HU, Linlin HU, Xin LI, Hongqiang QIU, Hua SHAO, Tongwen SUN, Yu WANG, Ping XU, Jing YANG, Yong YANG, Zhenwei YU, Bikui ZHANG, Huaijun ZHU, Xiaocong ZUO, Yi ZHANG, Liyan MIAO, and Jing ZHANG were consensus panel. All authors have read and approved the final manuscript.

Compliance with ethics guidelines

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