DR BRIAN T TSUJI (Orcid ID : 0000-0002-2413-2118)

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International Consensus Guidelines for the Optimal Use of the Polymyxins

Endorsed by the American College of Clinical Pharmacy (ACCP), Infectious Diseases Society of America (IDSA), International Society for Anti-infective Pharmacology (ISAP), Society of Critical Care Medicine (SCCM), and Society of Infectious Diseases Pharmacists (SIDP)

Brian T. Tsuji[1,*+], Jason M. Pogue[2+], Alexandre P. Zavascki[3], Mical Paul[4], George L. Daikos[5], Alan Forrest[6], Daniele R. Giacobbe[7], Claudio Viscoli[7], Helen Giamarellou[8], Ilias Karaiskos[8], Donald Kaye[9], Johan W. Mouton[10], Vincent H. Tam[11], Visanu Thamlikitkul[12], Richard G. Wunderink[13], Jian Li[14,¥], Roger L. Nation[15,¥], Keith S. Kaye[16,*,¥]

+: These authors contributed equally ¥: Joint senior authors

[1]School of Pharmacy and Pharmaceutical Sciences, University at Buffalo, State University of New York, Buffalo, New York, USA
[2]Detroit Medical Center, Detroit, MI
[3]Department of Internal Medicine,Medical School, Universidade Federal, do Rio Grande do Sul; Infectious, Diseases Service, Hospital de Clínicas, de Porto Alegre, Porto Alegre, Brazil
[4]Infectious Diseases Institute, Rambam Health Care Campus, Haifa, Israel; The Ruth and Bruce Rappaport Faculty of Medicine, Technion, Israel Institute of Technology, Haifa, Israel
[5]First Department of Propaedeutic Medicine, Laikon Hospital, Medical School, National and Kapodistrian University of Athens, Athens, Greece.
[6]Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA
[7]Infectious Diseases Unit, Ospedale Policlinico San Martino – Istituto di Ricovero e Cura a Carattere Scientifico per l'Oncologia, and Department of Health Sciences, University of Genoa, Genoa, Italy.
[8]1st Department of Internal Medicine, Infectious Diseases, Hygeia General Hospital, Athens, Greece.
[9]Drexel University College of Medicine, Philadelphia, Pennsylvania.
[10]Department of Medical Microbiology and Infectious Diseases, Erasmus MC, Rotterdam, The Netherlands
[11]University of Houston College of Pharmacy, Houston, TX, USA
[12]Division of Infectious Diseases and Tropical Medicine, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand.
[13]Division of Pulmonary and Critical Care, Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA.

[14]Monash Biomedicine Discovery Institute, Department of Microbiology, Monash University, Clayton, Victoria 3800, Australia.
[15]Drug Delivery, Disposition and Dynamics, Monash Institute of Pharmaceutical Sciences, Monash University, Parkville, Victoria 3052, Australia.
[16]Division of Infectious Diseases, University of Michigan Medical School, Ann Arbor, MI

*: Correspondence: Brian T. Tsuji, University at Buffalo, School of Pharmacy and Pharmaceutical Sciences, Buffalo, NY, 14203, Email: btsuji@buffalo.edu; Keith S. Kaye: Division of Infectious Diseases, University of Michigan Medical School, 5510A MSRB I, SPC 5680, 1150 W. Medical Center Drive, Ann Arbor, MI 48109-5680, USA. Electronic address: keithka@med.umich.edu;

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ABSTRACT

The polymyxin antibiotics colistin (polymyxin E) and polymyxin B became available in the 1950s, and thus did not undergo contemporary drug development procedures. Their clinical use has recently resurged assuming an important role as salvage therapy for otherwise untreatable gram-negative infections. Since their reintroduction into the clinic, there remains significant confusion due to the existence of several different conventions used to describe doses of the polymyxins, differences in their formulations, outdated product information, and uncertainties about susceptibility testing which has led to lack of clarity on how to optimally utilize and dose colistin and polymyxin B. In this publication, we report consensus therapeutic guidelines for agent selection and dosing of the polymyxin antibiotics for optimal use in adult patients, as endorsed by the American College of Clinical Pharmacy, Infectious Diseases Society of America, International Society of Anti-Infective Pharmacology, Society for Critical Care Medicine, and Society of Infectious Diseases Pharmacists. The European Society for Clinical Microbiology and Infectious Diseases endorses this consensus statement (Pending). We established a diverse, international expert panel to make therapeutic recommendations regarding the pharmacokinetic and pharmacodynamic properties of the drug and pharmacokinetic targets, polymyxin agent selection, dosing, dosage adjustment and

monitoring of colistin and polymyxin B, use of polymyxin-based combination therapy, intrathecal therapy, inhalation therapy, toxicity and prevention of renal failure. The treatment guidelines provide the first ever consensus recommendations for colistin and polymyxin B therapy which are intended to guide optimal clinical use.

INTRODUCTION

This practice guideline provides consensus recommendations pertaining to the clinical use of the polymyxin antibiotics, colistin (polymyxin E) and polymyxin B, for the treatment of bacterial infections in adults. The polymyxin antibiotics became available clinically in the 1950s, and thus did not undergo contemporary drug development procedures.[1] Polymyxins have a unique mechanism of action that involves disruption of the outer membrane integrity of Gram-negative bacteria, which in addition to providing rapid bactericidal activity, may enhance the activity of other antibiotic classes.[1] Their clinical use has recently resurged and the polymyxins have assumed an important role as salvage therapy for otherwise untreatable gram-negative infections, most notably multi-drug-resistant (MDR) and extensively drug-resistant (XDR) strains of *Pseudomonas aeruginosa*, *Acinetobacter baumannii and Enterobacteriaceae*.[2]

Since their reintroduction into the clinic in the 1980s through today there remains significant confusion regarding polymyxin use due to differences in the formulations (colistin is administered as an inactive prodrug, colistimethate (also known as colistin methanesulfonate, CMS), while polymyxin B is administered in its active form); the different conventions used to describe dosing of the polymyxins, particularly colistin; outdated product information; and, uncertainties regarding susceptibility testing.[3, 4] Thus, there remains a lack of clarity regarding how to optimally utilize and dose colistin and polymyxin B.[5, 6] Unfortunately, polymyxins are highly nephrotoxic agents and acute

kidney injury (AKI) occurs frequently with conventional doses.[7, 8] Given the narrow therapeutic windows (low therapeutic indices) of polymyxins, this guideline provides clinicians a practical framework for use in treating infections caused by MDR and XDR gram-negative pathogens.

METHODS

Consensus Panel Composition

The Consensus Panel was composed of international experts. They represent membership in the endorsing organizations (American College of Clinical Pharmacy [ACCP], the European Society for Clinical Microbiology and Infectious Diseases [ESCMID], the Infectious Diseases Society of America [IDSA], International Society of Anti-Infective Pharmacology [ISAP], Society of Critical Care Medicine [SCCM], and The Society of Infectious Diseases Pharmacists [SIDP].

Consensus Development Based on Evidence

Consensus Panel members were assigned key topics that contribute to current knowledge and optimal utilization of the polymyxins. A draft document addressing these areas that included specific recommendations was reviewed and approved by all Panel members. The Panel conducted face to face meetings and teleconferences to complete the guideline work. The purpose of the meetings and teleconferences was to determine and discuss the clinical questions to be addressed, assign topics for review and writing of the initial draft, and develop recommendations. The entire panel reviewed all sections. After review by members of ACCP, ESCMID, IDSA, SCCM, ISAP, and SIDP, the Panel reviewed the submitted comments and recommendations. After careful discussion and

consideration of these suggestions, the document was revised and circulated among the Panel and supporting societies for final approval.

Literature Review and Analysis

The recommendations in this guideline have been developed following a review of studies published before December 31, 2017 in English. Studies were identified through Library of Congress, LISTA (Library, Information Science & Technology Abstracts [EBSCO]), and PubMed database searches with no date restrictions using medical subject headings. Examples of keywords used to conduct literature searches were as follows: polymyxin, colistin, polymyxin B, nephrotoxicity, pharmacokinetics, pharmacodynamics, area under the curve, toxicodynamics, resistance, carbapenem, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*.

Process Overview

To evaluate evidence, the Panel followed a process consistent with other contemporary guidelines. The process for evaluation was based on the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system, which is a newly created system for grading the quality of evidence and strength of recommendations for healthcare.[9] Recommendations which were evaluated using the GRADE system were R21, R23, R24, R28, R31, R34, and R35. Some topics were determined to be ungradable such as those which involved nonclinical evidence (such recommendations for in vitro MIC breakpoints) and thus were not evaluated according to the GRADE criteria. Some recommendations were labelled as Best Practice Recommendations particularly in scenarios where the recommendations lack sufficient RCT evidence. Panel members were divided into groups consisting of a primary lead author and co-authors for each section. Each author was asked to review the literature, evaluate the evidence, develop and determine the strength of recommendations, and

provide an evidence summary supporting each recommendation. The Panel reviewed all recommendations, the assigned strength of the recommendations, and quality of evidence. Discrepancies were discussed and resolved. We acknowledge this as a potential limitation. Similar to other guidelines, some of the evidence utilized to establish the recommendations were published by the authors writing each section.

CLINICAL QUESTIONS AND RECOMMENDATIONS

Susceptibility and PK/PD

I. How should susceptibility be tested and what are the minimum inhibitory breakpoints for the polymyxins to guide therapy ?

Recommendation

R1. The joint European Committee on Antimicrobial Susceptibility Testing (EUCAST) and Clinical and Laboratory Standards Institute (CLSI) polymyxin breakpoint working group recommended that standard broth microdilution ISO-74 20776[10] be utilized as the reference method for the MIC testing of colistin and be performed with cation-adjusted Mueller Hinton broth, with sulfate salts of colistin in plain polystyrene trays without additives such as polysorbate-80.[11, 13] Agar dilution, disk diffusion, and gradient diffusion are not currently recommended by CLSI-EUCAST. We recommend that the CLSI/EUCAST joint working group clinical breakpoints be used for colistin (Table 1).

Table 1. CLSI/EUCAST Breakpoints for Colistin

Organism	Colistin MIC (mg/L)		
	Susceptible	Intermediate	Resistant
CLSI			
Acinetobacter spp.	≤2	--	≥4
Pseudomonas aeruginosa	≤2	--	≥4
Enterobacteriacieae*	≤2	--	≥4
EUCAST			
Acinetobacter spp.	≤2		>2
P. aeruginosa	≤2		>2
Enterobacteriaceae*	≤2		>2

CLSI = Clinical and Laboratory Standards Institute; EUCLAST = European Committee on Antimicrobial Susceptibility Testing; MIC = minimum inhibitory concentration.

*CLSI and EUCAST[11, 13] define insufficient clinical and PK/PD data to set a PK/PD-based breakpoint and cite epidemiological cut-off values (ECV, ECOFF) of 2mg/L.

Evidence Summary

CLSI[12] and EUCAST[14] established a Joint Working Group regarding susceptibility testing and breakpoints for colistin.[11,13] Polymyxin B was not addressed by this group. The CLSI/EUCAST Joint Working Group recommended clinical breakpoints which are harmonized for *Acinetobacter* spp. and *P. aeruginosa*. These recommendations were approved by the CLSI Antimicrobial Susceptibility Testing (AST) Subcommittee in 2016.[11,13] Breakpoints for Enterobacteriaceae were also considered. However, there were insufficient data and a clinical breakpoint was not established. Rather, an ECV was defined, based on the MIC distribution data for *Klebsiella aerogenes, Enterobacter cloacae, Escherichia coli, Klebsiella pneumoniae,* and *Raoultella ornithinolytica*. It is important to note that CLSI recommended that the epidemiological cutoff value (ECV) should be applied only to these species, as wild-type MIC distributions may be different for other genera and species of Enterobacteriaceae. Thus, the clinical breakpoints for colistin provided by the CLSI for *P. aeruginosa*, and *Acinetobacter* spp. were a susceptible breakpoint of ≤ 2mg/L and resistant breakpoint of ≥4mg/L.[13] EUCAST breakpoints for colistin for *P. aeruginosa*, and *Acinetobacter spp*. are a susceptible breakpoint of ≤2mg/L and resistant breakpoint of >2mg/L (Table 1).[14]

Future Research Needs

Research should be directed towards defining reliable testing methods for colistin that is more convenient than microdilution techniques. Rapid diagnostics of polymyxin

resistance[15-17] and defining Enterobactericeae MIC breakpoints are necessary. As Polymyxin B breakpoints have not been established, future research is necessary to independently evaluate and define clinical breakpoints for all species.

II. Is there a recommended PK/PD therapeutic target for maximization of efficacy for colistin and polymyxin B?

Recommendations

R2. We recommend that for colistin, an area under the plasma concentration-time curve across 24h at steady state ($AUC_{ss,24h}$) of ~50 mg*h/L is required, which equates to a target average steady-state plasma concentration ($C_{ss,avg}$) of approximately 2 mg/L for total drug and 1 mg/L for free drug as the protein binding is ~50%. While this target might be suboptimal for lower respiratory tract infections, it is noted that this should be considered as a maximum tolerable exposure, as concentrations higher than this have been shown to increase both the incidence and severity of AKI.

R3. We recommend similar targets for polymyxin B as those listed for colistin. However we note that data are lacking for an $AUC_{ss,24h}$ targets for polymyxin B. Emerging evidence suggests a different toxicodynamic (TD) profile for polymyxin B than colistin. There is some evidence that an $AUC_{ss,24h}$ target of 50-100 mg*h/L, corresponding to a $C_{ss,avg}$ of 2-4 mg/L, may be acceptable from a toxicity standpoint.

R4. We recommend that the aforementioned exposures for polymyxin B and colistin should be considered the maximal tolerable exposures. While these recommended exposures should achieve killing at the current MIC breakpoints based on the mouse thigh infection model, both colistin and polymyxin B when administered systemically (*i.e.*

not directly into the lungs) have been shown in the mouse lung infection model to be substantially less effective.

Evidence Summary

The *in vitro* activity of colistin and polymyxin B are virtually indistinguishable pharmacodynamically.[18-20] Both polymyxins demonstrate rapid bactericidal killing against susceptible strains of *P. aeruginosa*,[21, 22] *A. baumannii*,[18, 19] and *K. pneumoniae*[23, 24]. Concentrations above the MIC result in extremely rapid initial killing, with large decreases in colony forming units per mL (cfu/mL) occurring as early as 5 min following exposure. [17, 21] A modest post antibiotic effect is evident for high concentrations of colistin and polymyxin B.[17] The PK/PD linked parameter of the polymyxins has been investigated in *in vitro* pharmacokinetic models and animal models. Clearly, for colistin, *in vitro* [25, 26] and animal studies[27, 165] point to the free-drug area under the concentration-time curve to MIC ratio (*f*AUC/MIC) as the pharmacodynamic index that is best correlated with efficacy. Fewer preclinical data are available for polymyxin B[19, 20, 27, 28], however they also suggest that *f*AUC/MIC is the PK/PD index that correlates best with antibacterial activity. However, since colistin and polymyxin B have very similar molecular structures and *in vitro* activity [1],[29], it is reasonable to conclude that polymyxin B PK/PD indices and targets approach those of colistin.

Studies have elucidated the *f*AUC/MIC target for colistin in both *in vitro* systems and in animals. The most recent studies by Cheah et. al.[27] of systemically administered colistin against *A. baumannii* and *P. aeruginosa* in murine thigh and lung infection models have been used to determine *f*AUC/MIC targets for various magnitudes of bacterial kill and, as discussed above, to establish MIC breakpoints. For colistin the *f*AUC/MIC values to obtain a 2 $\log_{10}$ reduction in bacterial count in the experimental thigh

infection model ranged from 7.4 to 13.7 for *P. aeruginosa* and 7.4 to 17.6 for *A. baumannii.* The *f*AUC/MIC values to obtain a 1 $\log_{10}$ reduction in bacterial count in experimental thigh infection ranged from 6.6 to 10.9 for *P. aeruginosa* and 3.5 to 13.9 for *A. baumannii.* Target *f*AUC/MIC values for 1 and 2 $\log_{10}$ kill in the lung infection model were substantially higher. Indeed, for *A. baumannii* it was not even possible to achieve bacteriostasis for two of the three tested strains with the highest tolerable systemic dosage regimen of colistin.[30]

Based on these data, a target plasma colistin $C_{ss,avg}$ of 2 mg/L has been recommended for systemic administration of CMS.[6, 31, 32] This target is based on the following considerations. First, it accounts for the difference in the extent of protein binding between the plasma of mice and critically-ill patients.[6, 31, 32] The protein binding in humans is ~50%. Second, based on the thigh infection model this exposure would be expected to achieve bactericidal activity against an isolate with an MIC of 2 mg/L (the EUCAST and CLSI breakpoint). It is important to note that, unless the MIC of the infecting strain is well below the breakpoint, this target is very likely to be suboptimal for the systemic treatment of a lung infection[27, 28]. Third, it is considered unwise to target a higher plasma colistin $C_{ss,avg}$ because PK/TD analyses in patients have demonstrated that concentrations >2 mg/L are associated with an increase in both the incidence and severity of AKI.[33-35] Therefore, the proposed target concentrations of colistin should be considered the maximal tolerable target. Finally, even though a plasma colistin $C_{ss,avg}$ less than 2 mg/L may be adequate for an isolate with a low MIC, the susceptibility of the organism is often not known at the initiation of therapy and therefore a target of 2 mg/L is appropriate when commencing CMS. Furthermore, given inaccuracies with antibiotic susceptibility testing with the polymyxins, relying on the reported MIC may lead to suboptimal exposures.[166]

Landersdorfer et. al.[28] have recently reported the results of PK/PD studies for systemically administered polymyxin B against *K. pneumoniae* in murine thigh and lung infection models. The target values for 1 $\log_{10}$ reduction in bacterial count in the thigh model (*f*AUC/MIC 3.72-28.0) were similar to those for colistin for the same magnitude of bacterial kill. Unlike colistin, 2 $\log_{10}$ kill in the thigh model was not achieved even at the highest tolerated dose of polymyxin B. Similar to findings with colistin, polymyxin B was substantially less effective against lung infections and was not able to achieve stasis against any strain, even at the highest tolerated systemic dose.

For polymyxin B, there is a paucity of clinical PK/TD data and as described in detail below, it appears to differ from CMS with regard to the risk of AKI with currently used doses. In the absence of direct quantitative data to establish an exposure - toxicity relationship, clinicians should consider data derived from a recent meta-analysis of 16 studies involving a total of 971 subjects who received intravenous polymyxin B.[44] Pharmacokinetic exposures in patients in these studies were simulated based on patient characteristics and dosing information given in each study and published pharmacokinetic parameters for polymyxin B. The 25th, 50th and 75th percentiles of estimated polymyxin B AUC_{SS} were 46.7, 58.6 and 78.1 mg*h/L, respectively. Importantly, across all studies, 26.4% of patients displayed ≥50% decrease in creatinine clearance (CL_{cr}). Based on these findings some experts suggest a target $AUC_{ss,24h}$ as high as 100 mg*h/L for polymyxin B.[176] However, based on the recent lung infection model data for systemically administered polymyxin B against *K. pneumoniae*[28], these higher exposures may still be insufficient to achieve killing in respiratory tract infections. Thus, the benefit (and true toxicity risk) of these higher exposures remains unclear and therefore the panel recommends the same target exposures as for colistin (AUC_{SS} of ~50 mg*h/L).

It is important to note that the recommended PK/PD exposure targets have been derived from studies involving polymyxin monotherapy. Thus, the PK/PD targets should apply to polymyxin monotherapy. Recent Hollow Fiber Infection Model studies conducted in vitro using a high bacterial density of organism and in the absence of an immune system, have demonstrated a paradoxical effect for the polymyxins whereby higher doses of polymyxin B and colistin administered further amplified high level polymyxin resistance.[19, 22] An inoculum effect has been demonstrated for the polymyxin monotherapy with bacterial killing activity being significantly attenuated at inoculums consistent with ventilator-associated pneumonia (VAP) or health care–associated pneumonia (HAP). [19, 22]

Future Research Needs

Future research should be directed toward defining optimal exposure targets in critically ill patients to establish the relationship between polymyxin exposure in relation to clinical success and failure in this patient population. The high proportion of patients who fail polymyxin therapy, and other patient related factors, make the establishment of PK/PD relationships in critically ill patients extremely complex. PK/PD targets of polymyxins should also be considered in the context of combinations for future studies. The concentrations of polymyxins necessary to potentiate other agents would help determine if safer exposures can be given in combination regimens.

Polymyxin pharmacokinetics

III. Should I preferentially use one polymyxin over the other?

Recommendation:

R5. We recommend that it would be advantageous for clinicians to have access to parenteral products of both CMS and polymyxin B, so that they can choose between the two in particular circumstances.

R6. We recommend that polymyxin B should be the preferred agent for routine systemic use in invasive infections. The rationale for this recommendation is that Polymyxin B has superior PK characteristics in humans as well as a decreased potential to cause nephrotoxicity.

R7. We recommend that colistin should be the preferred polymyxin for the treatment of lower urinary tract infections given renal clearance of the prodrug CMS which then converts to the active moiety colistin in the urinary tract.

Evidence Summary

There are several clinical pharmacological differences between CMS/colistin and polymyxin B administered intravenously.[45, 46] We point the reader to an excellent review by Nation et. al. that highlight the key differences between polymyxin B and colistin by Nation et. al.[45, 46] Polymyxin B appears to have superior clinical PK characteristics for infections where it is important to rapidly and reliably achieve and then maintain a desired concentration in plasma. In critically ill patients receiving intravenous CMS, plasma concentrations of formed colistin rise slowly. Even with a loading dose of CMS at the initiation of therapy, it may take several hours to achieve plasma colistin concentrations that may be effective. Polymyxin B is not administered as a prodrug and therefore it is possible to use an intravenous dose to more rapidly achieve plasma concentrations that may be effective. In addition, dose selection is more difficult for CMS because the PK of CMS and formed colistin are subject to substantially greater inter-patient variability than occurs with polymyxin B.[45, 47] Moreover, in patients with good

renal function (creatinine clearance >80 mL/min) it is not possible to reliably attain a plasma colistin Css,avg of 2 mg/L, a concentration regarded as a reasonable initial target when MIC is unknown (see Section II)[6, 31, 32] even with daily doses of CMS at the upper end of approved doses (see Section VI) [6, 31]. The pharmacokinetics of polymyxin B are not similarly affected by renal function and therefore it is possible to reliably attain a plasma polymyxin B Css,avg of 2 mg/L with approved daily doses, even in patients with creatinine clearance >80 mL/min (see Section XI)[57, 80, 87, 88, 90].

The risk of AKI appears to be less with polymyxin B,[48-54] although some of the comparative studies are confounded by issues with experimental design[8]. Therapeutic drug monitoring (TDM) is inherently more difficult for colistin because of the need to ensure that samples are collected in such a way as to minimize ongoing *in vitro* conversion of CMS to colistin. However, CMS may be the preferred agent for the intravenous treatment of urinary tract infections. Urinary concentrations of colistin after administration of CMS (which is mainly cleared by renal excretion) can be high because of conversion of CMS to colistin in the urinary tract.[4, 46, 55, 56] In contrast, polymyxin B is predominantly cleared by non renal mechanisms with median urinary recovery of 4.0%.[57]

Future Research Needs

Although prospective randomized controlled trials (RCTs) comparing parenteral polymyxin B and colistin in patients with various types of infections are unlikely to be conducted , any comparative observational data would further elucidate the efficacy and toxicity differences between both polymyxins. In particular, well controlled safety and efficacy studies comparing dose-optimized colistin versus polymyxin B are of great interest.

Colistin Intravenous Dosing

IV. For CMS, what is the relationship between different dosing units in the literature?

Recommendation

R8. We recommend that hospital guidelines and prescription orders should specify doses of CMS in either number of international units (IU) or milligrams of colistin base activity (CBA), corresponding to the labelling convention used in the specific country. Because of the international scope of these guidelines, doses in the sections below are expressed in the approximate equivalents of both of these conventions. The conversion factor between the two conventions is: 1 million IU is equivalent to ~33 mg of CBA.

Evidence Summary

Colistin is administered parenterally in the form of the inactive prodrug, CMS. Unfortunately, two different conventions are used in different parts of the world to label vials of parenteral CMS and to express doses for patients. Both conventions are based upon microbiological assessment. The parenteral products of CMS available in Europe and some other parts of the world are labeled in terms of international units (IU). In contrast, parenteral CMS vials available in North and South America and many other parts of the world are labeled in terms of *colistin base activity* (CBA), which is another way of expressing microbiological activity.

One million IU corresponds to ~33 mg CBA. One million IU also corresponds approximately 80 mg of the chemical CMS.[58] Thus, it is critical that doses must not be prescribed in terms of milligrams of the chemical CMS.[4] When reading the scientific literature, clinicians must clearly understand whether doses reported in milligrams refer

to CBA or the chemical CMS. It is critical for consistent global reporting of colistin doses to promote safe and effective use.[59]

Future Research Needs

International Harmonization is urgently needed to have a consistent approach to specify all doses in either number of IU or milligrams of colistin base activity (CBA).

V. Do I need to administer an intravenous loading dose when I initiate therapy with CMS ?

Recommendation

R9. We recommend initiating intravenous therapy with a CMS loading dose of 300 mg CBA (~9 million IU) infused over 0.5-1 h, and administer the first maintenance dose 12-24 h later.

Evidence Summary

After initiation of CMS therapy in critically ill patients, plasma concentrations of formed colistin have been reported to increase slowly over many hours or even days,[32, 60-62] although more rapid increases have also been reported.[63] Such variation in the rate of concentration attainment of colistin probably is related to brand-to-brand or batch-to-batch differences in the complex chemical composition (degree of methanesulfonation) of the CMS administered to patients.[64] The case for a loading dose would be more compelling for a brand or batch that undergoes slow conversion. Unfortunately, there is no way of knowing (*a priori*) the rate of *in vivo* conversion for a particular batch. Thus, The impact of a loading dose on risk of developing AKI is unclear.[52, 54, 65] Considering the need for timely antibiotic administration, the therapeutic benefits of a loading dose may

justify the potential risk of loading-dose associated AKI[66-68]. The timing of the commencement of the maintenance dose should be based on the interval of the maintenance dose (e.g. if the patient is placed on every 12 hour colistin, the maintenance dose should start 12 hours later.)

Future Research Needs

More research is needed to define the brand-to-brand and batch to batch differences as they relate to degree of methanesulfonation and conversion to colistin. Additional data regarding the safety and efficacy of loading doses are needed.

VI. What should my initial daily maintenance dose of CMS be in patients with normal renal function?

Recommendation

R10. We recommend that for a patient with normal renal function, administer a daily dose of 300-360 mg CBA (~9-10.9 million IU), divided in two and infused over 0.5-1 h at 12 h intervals. Monitor renal function and adjust the daily dose accordingly using the recommendations in Table 2.

Evidence Summary

Determining initial daily maintenance dose requires consideration of the desired target average steady-state plasma concentration ($C_{ss,avg}$) of colistin. Based upon (a) translation of preclinical PK/PD data for *P. aeruginosa* and *A. baumannii* in murine thigh infection models and the ECV for *K. pneumoniae*; [11-13, 27, 69], (b) clinical PK/TD data defining the relationship between plasma colistin exposure and risk of AKI in patients;[33-35] and (c) the fact that the MIC of an isolate is often not known at initiation of therapy, a

target plasma colistin $C_{ss,avg}$ of 2 mg/L has been suggested.[6, 70] This target may be appropriate for treatment of relatively accessible infections with organisms having colistin MICs ≤2 mg/L. However, it is important to recognize that murine lung infections with *P. aeruginosa* and *A. baumannii* were substantially more resilient to systemic treatment than were murine thigh infections.[27] Thus, based on the preclinical data, a plasma colistin $C_{ss,avg}$ of 2 mg/L achieved *via* intravenous administration may not be adequate for the treatment of lung infections in critically ill patients, especially those caused by organisms that have elevated MIC organisms.[6, 27]

The daily doses of CMS to achieve a target plasma colistin $C_{ss,avg}$ of 2 mg/L (**Table 2)** have been proposed based upon analysis of PK data from over 200 critically ill patients with a wide range of renal function.[6] For patients with a creatinine clearance >90 mL/min, a suggested maximum dose of 360 mg CBA (~10.9 million IU) per day was proposed because of limited clinical experience regarding the rate and impact of AKI with daily doses above this level. Even with the daily doses proposed for patients with creatinine clearance >90 mL/min (**Table 2**), only 30-40% of patients are expected to achieve a plasma colistin $C_{ss,avg}$ ≥2 mg/L,[6, 62] although almost 80% of such patients may achieve a $C_{ss,avg}$ ≥1 mg/L.[6]

Table 2. "Look-up" Table of Daily Doses of CMS to Achieve a Desired Target Plasma Colistin Css,avg of 2 mg/L for Patients with Narrow Windows of Creatinine Clearance[a]

Creatinine clearance (mL/min)[c]	Daily dose of CMS for plasma colistin $C_{ss,avg}$ of 2 mg/L[b]	
	mg CBA per day	Million IU per day
0	130	3.95
5 to <10	145	4.40
10 to <20	160	4.85
20 to <30	175	5.30

30 to <40	195	5.90
40 to <50	220	6.65
50 to <60	245	7.40
60 to <70	275	8.35
70 to <80	300	9.00
80 to <90	340	10.3
≥90	360	10.9

CMS = colistin methanesulfonate; $C_{ss,avg}$ = average steady-state plasma concentration; CBA = colistin base activity.

[a] Reproduced from Nation *et al.*[6] with minor modification.

[b] Daily dose administered in two divided doses 12 h apart.

[c]Adjusted body weight should be utilized for creatinine clearance estimation.

While weight-based dosing algorithms have been proposed as alternatives to the US package insert, such as those in a current randomized controlled trial of colistin , https://clinicaltrials.gov/ct2/show/NCT01597973,[71] PK data do not support the need for weight-based dosing.

Future Research Needs

The dose suggestions in **Table 2** require validation by independent studies. In particular, these recommended doses need to be compared to lower historical dosing regimens to ensure that the appropriate balance between safety and efficacy is achieved. Research is needed to define optimal dosing strategies in patients with creatinine clearance >80 mL/min.

VII. Do I need to adjust the daily maintenance dose of CMS if the patient has renal impairment?

Recommendation

R11. We recommend that CMS dose adjustments be made in patients with renal insufficiency as provided in **Table 2.**

Evidence Summary

The apparent clearance of colistin and hence the plasma colistin $C_{ss,avg}$ achieved from a given daily dose of CMS is influenced by kidney function.[6, 32, 63] Therefore, the daily dose of CMS to target a plasma colistin $C_{ss,avg}$ of 2 mg/L should be adjusted for renal impairment. Daily doses for patients with various degrees of renal function are provided in Table 2. The daily dose is divided into two doses, administered 12 hours apart, and each dose is infused over 0.5-1 hour. If the daily dose is not reduced in patients with decreased renal function, there is an increased probability that the plasma colistin Css,avg will be higher than 2 mg/L. This would be expected to increase antibacterial activity but is also expected to increase the likelihood of AKI.

Future Research Needs

Although it is critical to adjust colistin doses in patients with renal impairment,definitive knowledge of the subsequent concentrations obtained requires therapeutic drug monitoring (TDM). Research is required to investigate the optimal approach to implementing TDM, including identification of the patient groups most likely to benefit.

VIII. Does renal replacement therapy have implications for selection of intravenous CMS dosage regimens?

Recommendation

R12. We recommend that in order to target a plasma colistin $C_{ss,avg}$ of 2 mg/L in a patient on *intermittent hemodialysis (IHD)*, the following dosing schedule be utilized: On a non-dialysis day administer a CMS dose of 130 mg CBA per day (~3.95 million IU per day). On a dialysis day, administer a supplemental dose of CMS 40 mg CBA (~1.2 million IU) or 50 mg CBA (~1.6 million IU) for a 3 or 4 h IHD session, respectively. If possible, the supplement to the baseline (non-dialysis) daily dose should be administered with the next regular dose, after the dialysis session has ended. Conduct IHD sessions as late as is possible within a CMS dosage interval to minimize the amount of CMS and formed colistin lost to the extracorporeal system.

R13. We recommend that in order to target a plasma colistin $C_{ss,avg}$ of 2 mg/L in *patients prescribed sustained low-efficiency dialysis (SLED)*, that 10% of the CMS dose be added to the baseline daily dose per 1 h of SLED.

R14. We recommend that for patients prescribed continuous renal replacement therapy (CRRT), for a plasma colistin $C_{ss,avg}$ of 2 mg/L to administer CBA 440 mg per day (~13 million IU per day).

Evidence Summary

CMS and formed colistin are efficiently cleared by intermittent and continuous renal support modalities; less information is available for sustained low efficiency dialysis (SLED) than for shorter forms of intermittent hemodialysis (IHD) and continuous renal replacement therapy (CRRT).[6, 32, 72-79] Supplemental doses of CMS are needed for patients receiving IHD or SLED. In general hemodialysis, SLED, and CRRT each remove ~10% of colistin an hour necessitating replacement of 10% of the daily dose per hour on these modalities. As the duration of CRRT (24 hours) is greater than the

duration of SLED (often 8-10 hours) which is greater than the duration of IHD (3-4 hours), the supplemental doses needed differ significantly as a function of dialysis type. Apparent clearance of colistin and hence the dose requirements of CMS are greater in patients on CRRT than for patients with normal renal function.[6, 32, 78] Detailed dose suggestions for patients receiving renal support have been proposed.[6, 77, 78]

For target a plasma colistin Css,avg of 2 mg/L in patients prescribed sustained low efficiency dialysis (SLED), it is recommended that 10% be added to the baseline daily dose per 1 h of SLED, we provide the following practical example is illustration in the following.

For a patient receiving a 10-h nocturnal SLED session each day and receiving CMS every 12 h:

- For a patient with CLcr of approximately 0 ml/min, the CMS Dose would be the sum of the baseline CMS Dose (CBA dose of 130 mg/day [~3.95 Million IU/ day], Table 2) plus a supplemental dose comprising 10% of the baseline dose per h × 10 h.
- That is, for this case, the CBA dose would be 260 mg per day (~7.9 million IU per day). In such a case, it may be most convenient and safe to administer 130 mg CBA (~3.95 million IU) every 12 h.

Future Research Needs

Research is needed on colistin dosing in SLED patients particularly with regard the impact of different dialysis membranes on colistin removal. The above recommendations for SLED were based on small sample sizes with the use of medium to high flux filters. Removal would be expected to be decreased with lower flux filters.

Polymyxin B Intravenous Dosing

IX. Do I need to administer an intravenous loading dose when I initiate therapy with polymyxin B ?

Recommendation

R15. We recommend a loading dose of 2.0 to 2.5 mg/kg for polymyxin B based on total body weight (TBW) (equivalent to 20,000 to 25,000 IU/kg) over 1 h.

Evidence Summary

A population PK study in critically ill patients showed that with a regimen of 1.25 mg/kg (equivalent to 12,500 IU/kg) every 12-hours, plasma polymyxin B concentrations achieved after the first dose were approximately 56-70% of the concentrations observed at steady state.[80] Using Monte-Carlo simulations, it was estimated that with a loading dose of 2.0 mg/kg (equivalent to 20,000 IU/kg), day 1 exposures would likely be 76-94% of exposures at steady state.[80] There is a paucity of data regarding the clinical safety and efficacy of a polymyxin B loading dose strategy. However, one analysis found no association between loading dose of either polymyxin B or colistin and nephrotoxicity (adjusted Hazard Ratio 0.78, 95% Confidence Interval 0.42 - 1.46).[54] In this analysis, 36 patients received an average polymyxin B loading dose of 1.9 ± 0.5 mg/kg.[54] Conversely, although not statistically significant, loading doses have been more frequently administered in patients who presented with neurotoxicity compared to patients who did not present with this adverse event (2 out 6 [33.3%] and 7 out 68 [10.3%], respectively; P=0.15).[83]

Although it is reasonable to administer loading doses to all patients, priority should be given to those that are critically ill such as those with sepsis or septic shock. PK data does not support capping upper absolute dose (i.e. expressed in milligrams) in

obese patients. However, experience with the administration of >200 mg per infusion is limited,[81, 83] and infusion-related adverse effects, which include sudden thoracic pain, paresthesias, dizziness, dyspnea and hypoxemia, were reported at a crude incidence of 0.9% (95% CI 0.2 to 3.2%) and may increase with such doses.[83]

Future Research Needs

Additional research is needed to define the safety and efficacy of high initial dose polymyxin B regimens. Although administration of doses >3 mg/kg (equivalent to 30,000 IU/kg) has been reported in patients[57, 83], more data are needed on the safety as well as clinical and microbiological impact of these regimens.

X. What is the recommended initial daily maintenance dose for polymyxin B in patients with normal renal function?

Recommendation

R17. We recommend that for patients with severe infections, a polymyxin B dose of 1.25 to 1.5 mg/kg (equivalent to 12,500 to 15,000 IU/kg TBW) every 12 hours infused over 1 hour.

Evidence Summary

As discussed above, considering that *f*AUC/MIC targets for 1 $\log_{10}$ kill for polymyxin B against *K. pneumoniae*[28] showed generally good agreement with the corresponding values for colistin against *P. aeruginosa* and *A. baumannii* in the murine thigh infection model[27], and given the similar plasma unbound fractions (i.e. ~0.50) of polymyxin B[57] and colistin[84] in humans, a $C_{ss,avg}$ of 2 mg/L seems to be an appropriate target for polymyxin B dosing guidance. This target may be revised as more information

becomes available from preclinical studies to inform PK/PD relationships against Gram-negative pathogens and from clinical studies to inform the PK/TD relationship for nephrotoxicity.

With doses of 2.5 and 3.0 mg/kg/day (equivalent to 25,000 to 30,000 IU/kg/day, respectively), 90% of patients, as determined by Monte Carlo simulations, would be expected to achieve an AUC of polymyxin B at steady state of at least 44.3 and 53.1 mg*h/L, respectively,[80] which correspond to $C_{ss,avg}$ of 1.8 and 2.2 mg/L, respectively. Thus, against isolates with polymyxin B MICs of 2 mg/L, the PK/PD target for 1 $\log_{10}$ kill of *P. aeruginosa*, *A. baumannii* and *K. pneumoniae* in murine thigh infection[27, 28] will have an estimated probability of target attainment (PTA) of >90% with either dosing strategy. Given the aforementioned concerns with antibacterial activity of systemically administered polymyxins in lung infections[27, 28], higher plasma concentration targets might be necessary to achieve adequate antimicrobial activity in different infection sites. However, due to the lack of clinical safety data, a maintenance dose >3 mg/kg/day (equivalent to 30,000 IU/kg/day) cannot be recommended at this time. A target of 2 mg/L is recommended even for isolates with an MIC <2 mg/L in patients with severe infections.[85] Unfortunately, in the routine clinical microbiology laboratory setting, the MIC cannot be determined with enough accuracy at this stage, and a target of 2 mg/L therefore seems to be prudent in all cases.

PK data does not support capping upper absolute doses (i.e. expressed in milligrams) in patients with high TBW. However, experience with infusions of >200 mg remains limited[81, 83] and infusion-related adverse effects may increase with such doses.

There is no specific recommendation in the package insert concerning the duration of infusion. However, in recent PK analyses reflecting real world use of polymyxin B, doses were safely administered over 1 to 4 hours in most patients.[80, 86-88] Since there might be a potential benefit on renal toxicity of higher peak-to-trough

differences,[89] infusions over 1 hour might be preferred over longer infusions, if well tolerated by patients.

Future Research Needs

Additional research is needed to define the safety and efficacy associated with optimal maintenance dosing of polymyxin B.

XI. Do I need to adjust the daily polymyxin B maintenance dose if the patient has renal impairment?

Recommendation

R18. We recommend that daily maintenance doses of polymyxin B should not be adjusted if the patient has renal impairment.

Evidence Summary

Polymyxin B is not significantly eliminated by the kidneys, and clinical PK studies demonstrate that polymyxin B clearance is not dependent on creatinine clearance.[57, 80, 87, 88, 90] Therefore, there is no PK rationale for adjusting doses according to the renal function. Lowering doses in patients with decreased creatinine clearance will lead to lower polymyxin B plasma concentrations. The package insert for polymyxin B recommends dose reducing "downward for individuals with kidney impairment", however, it is unclear what data spurred this recommendation.[177] More recent PK data as well as enhanced understanding of renal handling of polymyxin B refutes this recommendation. If unnecessary renal dose adjustments are made in patients there is potential for drug underexposure, and clinical failure. Clinical literature supports this

claim, as doses ≤1.2 mg/kg/day (equivalent to ≤12,000 IU/kg/day), which were commonly prescribed to patients with renal insufficiency, have been associated with increased mortality in patients receiving polymyxin B.[85]

Future Research Needs

Package insert dose adjustment for renal impairment should be revised since it is not supported by modern PK data. Furthermore, larger pharmacokinetic studies in patients with renal insufficiency are needed to validate the recommendations provided herein.

XII. Does renal replacement therapy have implications for selection of intravenous polymyxin B dosage regimens?

Recommendation

R19. We recommend that neither the loading dose nor maintenance dose be adjusted in patients receiving RRT.

Evidence Summary

There are only two reports of the PK of polymyxin B in patients receiving renal replacement, and both involved CRRT. The first report involved two patients receiving continuous venovenous hemodialysis (CVVHD)[81] while the second described a patient receiving continuous venovenous hemofiltration (CVVHF).[91] In the former two patients the CVVHD was responsible for 5.6% and 12.2% of polymyxin B total body clearance[81] while in the latter patient the polymyxin B extraction across the extracorporeal cartridge was only 5.0%.[91] This degree of elimination is similar to the extent of renal elimination in critically ill patients not receiving extracorporeal modalities (median 4%, range 1.0 - 17.4%). Although data are limited to these three cases, they suggest that CVVHD and

CVVHF will not remove more than 12% of total body polymyxin B, similar to percentage recovered in the urine in patients not requiring renal replacement therapy.[57] Thus, on the basis of these PK data dose modifications are not warranted in patients receiving these forms of CRRT.

Clinical data also suggest that dose reductions in patients on CVVH can potentially lead to underexposure and increased risk for poor outcomes[92]. Higher total daily doses were associated with lower 30-day mortality in bivariate analysis (p=0.04) and a total daily dose ≥200 mg (equivalent to ≥2,000,000 IU) was associated with a lower risk for 30-day mortality in multivariate analysis (p=0.02).[92] Thus, dose reductions for patients receiving renal replacement therapy are not only unwarranted due to limited pharmacokinetic data, but the clinical evidence suggests they might potentially be harmful to patients.

There are currently no PK data on polymyxin B in patients receiving intermittent renal replacement therapy; however, based on non-renal clearance of polymyxin B, administration of non-adjusted doses has been reported.

Future Research Needs

PK data are lacking for polymyxin B in patients receiving IHD and SLED, and only minimal data are available for CRRT. Larger pharmacokinetic analyses are urgently needed to further refine dosing recommendations.

XIII. Is there a role for therapeutic drug monitoring of colistin or polymyxin B ?

Recommendation

R20. We recommend that therapeutic drug monitoring (TDM) and adaptive feedback control (AFC) should be used wherever possible for both colistin and polymyxin B.

Evidence Summary

The polymyxins display characteristics that suggest that TDM and AFC would be beneficial. Drug dose cannot be safely optimized using clinical observation and dosing algorithms alone, especially in the early treatment period that is a critical determinant of prognosis. Moreover, if therapy is unsuccessful there are potential dire consequences (clinical ones for the patient concerned in addition to emergence of polymyxin resistance). In addition, based on the more abundant data for colistin: (a) there are established relationships between plasma exposure and both antibacterial effect[27] and risk of AKI[57, 62, 84]; (b) the therapeutic window is extremely narrow since plasma exposures required for antibacterial effect overlap those associated with increased AKI risk[84]; and, (c) there is substantial inter-patient variability in PK that cannot be accounted for by known patient factors (such variability is substantially greater for intravenous colistin than polymyxin B)[57, 62, 84].

The use of TDM as an aid to dosing CMS has been reported for a small number of patients[163, 164], but the benefit has not been demonstrated in appropriately designed studies[3]. For colistin, it is essential to ensure that sample collection, handling and analysis are conducted appropriately to minimize *ex vivo* conversion of CMS to colistin[32, 60]. For colistin, by collecting blood samples just prior to the next dose (when CMS concentrations are the lowest) the potential for measurement of artificially elevated plasma colistin concentrations is minimized, but not eliminated. For polymyxin B sample collection, handling and analysis for TDM is substantially less complicated because this polymyxin is administered directly, not as an inactive prodrug. As stated above, using TDM the target concentration is 2 mg/L for susceptible micro-organisms, irrespective of the MIC provided by the routine clinical microbiology laboratory.

Future Research Needs

Real-time PK/PD/TD profiles obtained from patients during polymyxin therapy are needed so that maximally precise, patient-specific PK information can be obtained. Such data would inform evolving dose optimization at the individual patient level.

XIV. What strategies can be employed to decrease the incidence of acute kidney injury in patients receiving colistin or polymyxin B therapy?

Recommendations

R21. We recommend that wherever possible, concomitant nephrotoxic agents should be avoided in patients receiving colistin or polymyxin B (*Strong recommendation, moderate quality evidence*)

Remark: This recommendation was initially graded with low confidence because data were observational in nature. However, the evidence quality was upgraded due to the consistent large magnitude of the effect of administration of concomitant nephrotoxins on the incidence of AKI with no important threats to the validity of the data

Evidence Summary

Undoubtedly, nephrotoxicity is the most clinically relevant and dose-limiting adverse reaction of the polymyxins. The incidence of nephrotoxicity varies widely in the literature from 0 to >60% largely due to heterogeneous patient populations, differing definitions of nephrotoxicity, wide ranges of polymyxin doses administered, and differences in both severity of illness and the presence/absence of various other risk factors of the patients being studied.[33, 35, 50, 54, 93, 99, 100, 101] Contemporary studies, using commonly accepted polymyxin doses and AKI definitions place the rate of associated nephrotoxicity in the 20-50% range for both polymyxins. [33, 35, 50, 54, 93, 99, 100, 101]

Risk factors vary between studies but there are a few common factors identified throughout the literature. More advanced age has been identified as a risk factor in multiple analyses, although the "cutoff" age for increased risk is inconsistent. Weight, irrespective of dose given, has been shown to be a risk factor for nephrotoxicity for both colistin[93] and polymyxin B[94]. Chronic comorbid conditions and the presence of hypoalbuminemia have been reported as risk factors for nephrotoxicity[93, 94]. While these factors can help clinicians identify those patients at highest risk for AKI while receiving polymyxin therapy, they are not modifiable. Clinicians should work to address modifiable risk factors for AKI and the recommendations represent the panel's view regarding how best to accomplish this.

Receipt of concomitant nephrotoxic agents is a consistent risk factor for AKI in patients receiving polymyxin therapy. While many nephrotoxins have been identified as potential risk factors, only a few would be considered modifiable. For example, receipt of calcineurin inhibitiors, acute administration of loop diuretics, and vasopressors have all been associated with polymyxin-associated nephrotoxicity; however these exposures often cannot be avoided. Conversely, the use of IV contrast media for diagnostic testing, administering nonsteroidal antiinflammatory drug or angiotensin-converting enzyme inhibitor therapy, and/or receipt of other nephrotoxic antibiotics, most notably vancomycin, should be assessed by clinicians and when possible, avoided.[96, 97] While combination therapy with colistin and vancomycin has shown both *in vitro* synergy[95] and select clinical data suggest a potential clinical benefit of this combination[96, 97], multiple analyses with both colistin[97, 98] and polymyxin B[99] have shown concomitant vancomycin to be an independent predictor of polymyxin-associated AKI; thus this combination should be avoided. Additionally, analyses have demonstrated rifampin[100] co-administration to increase the risk for nephrotoxicity. Furthermore, concomitant

aminoglycosides have also been identified as independent predictors of colistin-associated AKI[101]. Given the emergence and spread of XDR Gram-negative bacteria, including carbapenem-resistant Enterobacteriaceae (CRE), we acknowledge that aminoglycosides frequently are often one of the few agents to which these organisms are susceptible and combination therapy involving aminoglycosides and polymyxins might be an attractive alternative and in some cases might be unavoidable.

Future Research Needs

Data demonstrating the impact of purposeful avoidance of the nephrotoxic agents described above on prevention of AKI are lacking. Such data would enhance the quality of the evidence supporting this recommendation. Future research is needed evaluating the safety and efficacy of polymyxin + aminoglycoside therapy. Timely monitoring of renal function is a critical aspect of detecting AKI for the polymyxins. As such, further research on biomarkers that respond rapidly to renal insult would be highly beneficial for toxicodynamic optimization.

R22. We recommend that doses greater than those listed in this guideline for colistin or polymyxin B be avoided in the absence of TDM (*Best practice recommendation)*.

Remark: This recommendation was not assessed using GRADE. There is an absence of data testing this strategy. There are theoretical advantages to higher doses but the comparative safety and efficacy of those are unavailable based on the currently available literature. This recommendation prioritizes safety, due to the absence of efficacy data with higher dosing strategies. Furthermore, while dose increase or decrease based on serum concentrations is rational from a pharmacokinetic,

pharmacodynamic and toxicodynamic standpoint, there is an absence of data assessing the safety and efficacy of such a strategy.

Evidence Summary

The most important risk factor for polymyxin-associated AKI is the magnitude of polymyxin exposure. Higher CMS doses are consistently identified as a risk factor, with CBA doses >5 mg/kg/day (equivalent to ~165,000 IU/kg/day) consistently posing the highest risk. Similarly, associations have been seen with absolute polymyxin B doses ≥150, 200[102], and 250[85] mg/day. Not surprisingly, colistin serum steady-state concentrations have also been associated with AKI. Average steady-state concentrations of 1.9 - 2.3 mg/L have been associated with higher degrees of toxicity than lower concentations[34] whereas day 3 trough concentrations of ≥ 3.33 and 2.42 mg/L have been associated with AKI at days 7 and 14, respectively[33]. Importantly, in the latter study, of the 26 patients who had colistin trough values >2.2 mg/L on day 3, 17 (65%) and 22 (85%) had toxicity at days 7 and 14, respectively[33]. These toxicodynamic studies serve as the basis of the maximal tolerable dose described in earlier recommendations in these guidelines and we would recommend against giving higher exposures.

Future Research Needs

Studies are needed that weigh the risk-to-benefit ratio of clinical cure of infection with the development of nephrotoxicity. Furthermore, investigation regarding dosing regimens (i.e. once daily, multiple times daily or continuous infusions) or other novel dosing strategies and their impact on nephrotoxicity should also be undertaken.

R23. In countries where both agents are available, we recommend preferential use of polymyxin B to limit the rate of polymyxin-associated AKI. (*Weak recommendation, low quality evidence*)

Remark: This recommendation started with low quality evidence given the observational data used to make the recommendation. The confidence for the recommendation could not be significantly upgraded or downgraded based on the evidence. The relative consistency of the findings of the published data literature, and the consistent large magnitude were considerations for upgrading the strength of the quality of the evidence. However, these were counterbalanced by some of the data which did not show a safety advantage with polymyxin B. Data from Phe et. al.[103] demonstrated that polymyxin B was not found to be more nephrotoxic than colistin. Additionally, comparative studies are also confounded by the different doses of colistin and polymyxin B utilized in comparing AKI. A strong recommendation cannot be made until adequately powered prospective, dose-optimized studies are performed.

Evidence Summary

When polymyxins re-emerged in the 1980s one of the main drivers of preferential use of CMS over polymyxin B was the historical belief, driven by anecdotes rather than evidence, that colistin was the safer option with respect to nephrotoxicity. Modern day data have debunked this belief, and interestingly there is a suggestion that polymyxin B might in fact be safer, with respect to the kidneys, than colistin. Data from kidney cell lines[103] as well as animals[104] suggest that polymyxin B and colistin, as would be expected from their similar chemical structures, have similar toxic effects on the kidney.

However, in the six currently available clinical studies assessing comparative nephrotoxicity rates between the polymyxins, five have displayed at least some suggestion of increased and/or more severe nephrotoxicity with colistin. The one outlier to this trend was limited by small numbers (only 30 and 39 patients receiving polymyxin B and CMS were evaluable for AKI, respectively).[48, 49, 105, 103, 52, 54] We would like to point the reader to a recent systemic review and meta-analyses by Falagas et. al. which summarizes the published studies.[45] Taken together, these data suggest that polymyxin B is associated with less AKI in patients.

Regardless of the mechanism, the current data, while limited in quality, suggest that polymyxin B is less likely to cause nephrotoxicity than CMS. Until further evidence becomes available clinicians should consider polymyxin B as the preferred alternative to decrease risk for polymyxin-associated AKI. An exception to this would be for the treatment of urinary tract infections, where CMS/colistin may be the preferred agent.

Future Research Needs

The main areas for prioritization of future research include prospective comparative trials assessing AKI rates with dose-optimized polymyxins, investigation into the mechanisms of potential discordant toxicity rates between the agents, and finally whether dose-optimized polymyxins differ in their rates of non-nephrotoxic adverse reactions, most notably neurotoxicity. Additionally, studies comparing neurotoxicities and skin hyperpigmentation for polymyxin B versus colistin require future studies.

R24. Until further data become available, we do not recommend the routine use of antioxidants for the primary purpose of reducing polymyxin-associated nephrotoxicity (*Weak recommendation, very low quality of evidence*)

Remark: The quality of the evidence was initially low given that both underpowered randomized controlled and observational data were used for the assessment. The data suffered from every potential reason for downgrading the data (risk of bias, inconsistency, indirectness, imprecision, and publication bias), and therefore were rated as very low quality of evidence. The recommendation was weak, given that there are animal data to support a potential protective effect as well as the general lack of risk of patient harm with administration of antioxidants.

Evidence Summary

There has been increased interest in using antioxidants, most notably ascorbic acid, as a nephroprotective mechanism in patients receiving polymyxin therapy. This stems from preclinical observations that in polymyxin-induced nephrotoxicity, oxidative stress from reactive oxygen species initiates renal cell apoptosis. Animal models have supported this protective role of ascorbic acid by demonstrating that administration can decrease kidney tissue apoptosis and subsequent tubular damage[106].

Clinical data exploring the impact of ascorbic acid on limiting nephrotoxicity are scarce and have displayed conflicting results. Dalfino et. al.[107] recently assessed nephrotoxicity rates with a novel dosing regimen based on recent pharmacokinetic advances. Interestingly, although not the primary intent of the analysis, both bivariate (30% vs. 67%; $p < 0.05$) and multivariate analyses (adjusted odds ratio 0.27, 95% CI 0.13 - 0.57) suggested that concomitant administration of ascorbic acid was protective against nephrotoxicity. Conversely, a small RCT in 28 patients, failed to show any benefit of 4 ascorbic acid grams/day on the rates of colistin-associated nephrotoxicity[108]. Therefore, while a promising therapy, the current data are insufficient to warrant a recommendation in favor of routine administration of ascorbic acid or any other antioxidant for the prevention of polymyxin-associated AKI.

Future Research Needs

Adequately powered and sufficiently controlled prospective studies are warranted to assess the impact of ascorbic acid or other antioxidants on the incidence and/or severity of polymyxin-associated nephrotoxicity.

XV. If my patient develops AKI while on colistin or polymyxin B, should I decrease the dose?

Recommendations

R25. We recommend that if a patient develops AKI while on colistin the daily dose should be decreased to the appropriate renally-adjusted dose for a plasma colistin $C_{ss,avg}$ of 2 mg/L. (**Table 2**).

R26. We recommend that doses should not be decreased, outside of the renal dosing recommendations for colistin, particularly in patients who develop AKI when colistin or polymyxin B is being administered for a life-threatening infection, a deep-seated infection, or when the infecting pathogen has an MIC >1 mg/L *(strong recommendation, low quality evidence).* If the MIC of the infecting pathogen and/or the nature of the infection suggest that targeting a lower plasma concentration may be adequate, consideration should be given to decreasing the dose to target a different $C_{ss,avg}$ of colistin (*Best practice recommendation)*

R27. We recommend that cessation of therapy may be considered in patients who develop AKI if infection diagnosis is uncertain or when there is an alternative less nephrotoxic drug available. *(Best practice recommendation)*

Evidence Summary

While clinical PK data support the need for dose adjustment in AKI for colistin they do not for polymyxin B[57, 87]. Although it is a reasonable hypothesis that patients who develop AKI have 'supra-therapeutic' polymyxin plasma concentrations, evidence from colistin studies suggests considerable overlap between the 'therapeutic' and 'nephrotoxic' plasma concentrations of polymyxins among patients who develop AKI[33-35]. It is also important to note that AKI may be precipitated by sepsis arising from inadequate treatment of infection[109].

The rationale for the recommendation to not lower doses of polymyxin B in the setting of a decline in renal function is that lowering doses in these patients will ultimately lower serum concentrations of polymyxin B, and while that might limit toxicity, there is a greater concern that it would compromise therapeutic efficacy as has been demonstrated in published studies. For polymyxin B there are data suggesting that higher doses, even in the setting of AKI, improves outcomes. One retrospective study with 276 patients showed a lower risk for in-hospital mortality (adjusted odds ratio, 0.43; 95% CI, 0.23-0.79; p=0.007) in patients receiving high-dose polymyxin B (≥200 mg/day) despite the development of moderate or severe renal injury, defined as ≥100% increase in serum creatinine from baseline or need for hemodialysis. In a larger multicenter, prospective cohort with 410 patients, a polymyxin dose ≥150 mg/day was associated with a non-significant protective effect on 30-day mortality (adjusted hazard ratio, 0.74; 95%CI, 0.51–1.07; p=0.11) in patients who developed AKI according to RIFLE criteria.

In patients who have less severe infections, that are clinically stable, and patients that are receiving combination therapy, or those with infecting organisms with MICs ≤ 1 mg/L, it is reasonable to reduce the dose in the setting of AKI. For such patients receiving colistin, a lower steady-state plasma concentration may be targeted by making proportional adjustment to the daily doses in Table 2 or by using the reported dosing

algorithm[84]. Because the process regarding how to exactly achieve this and evidence to support this strategy is lacking, we find it reasonable to modify the dose to target a steady state concentration of 1.5 mg/L in certain clinical scenarios. A similar strategy can be used for polymyxin B.

For polymyxin B, in similar clinical scenarios as described above for colistin, it would be reasonable to decrease the dose to the lower end of the package insert range. While the evidence to support this strategy for polymyxin B and colistin is currently lacking, it is considered appropriate in these settings as the likelihood of achieving only sub-therapeutic drug exposure is significantly diminished and continued declines in renal function might adversely impact clinical outcomes. Similarly, clinical judgement should be used to decide whether or not to continue polymyxin therapy in patients who develop AKI and have an unconfirmed microbiological infectious etiology. The potential benefit of maintaining treatment should be weighed against the risk of worsening AKI on a case-by-case basis.

Future Research Needs

Although research is emerging regarding the association between exposure of colistin and polymyxin B and toxicity, the precise toxicodynamic profile has yet to be fully elucidated as it relates to the time frame and onset of nephrotoxicity. Therefore, future research needs to further elucidate these targets. Furthermore, data pertaining to clear dose modifications in the setting of AKI, and the impact it has on the progression and/or resolution of AKI and clinical efficacy are urgently needed.

POLYMYXIN COMBINATIONS

Polymyxin combination therapy is a heavily debated and controversial topic. There are multiple reasons that combination therapy might be advantageous. First, it is now very clear that plasma concentrations of colistin are sub-optimal in a substantial proportion of patients, even when daily doses of CMS are at the upper limit of the approved product label.[32, 60-62, 84] Similarly, plasma polymyxin B concentrations achieved among patients receiving the current upper limit daily dose are not likely to be reliably efficacious in many clinical scenarios, including respiratory tract infections.[57] Second, it is not possible to simply increase the daily doses of CMS or polymyxin B beyond doses recommended in this document due to the potential for nephrotoxicity which is the major dose-limiting adverse effect.[8, 52, 100] Third, is the emerging body of evidence in preclinical lung infection models that suggest poor *in vivo* response to the polymyxins.[27, 28] Finally, polymyxin resistance is increasing worldwide with several recent reports of clinical failure due to emergence of resistance during monotherapy.[110, 111] With the recent report of mobile colistin resistance genes,[15-17] the presence of heteroresistance[18] and the association between colistin resistance and increased risk for in-hospital mortality[110], there is mounting support for strategies to therapeutically optimize polymyxins, including combination therapy. There is a mechanism-based rationale for using polymyxins in combination with other antimicrobials which display synergy with a membrane permeabilizer (such as the polymyxins) allowing for increased concentrations of companion antibacterial agents that have intracellular targets.[112-115]

Unfortunately, the clinical literature on combination therapy *versus* monotherapy is difficult to interpret due to limitations in many studies.[116] The first type of limitation relates to the characteristics of the critically ill patient population that develop infections due to carbapenem-resistant Gram-negative bacilli. These are generally complex patients, with pre-existing comorbitidies who experience extremely high rates of

treatment failure and death irrespective of infection-related outcome. Since the primary outcome in many analyses is all-cause mortality, defining the effectiveness of combination- *vs*. mono-therapy based on this outcome is extremely challenging. In addition, patients requiring polymyxin therapy frequently have significant delays in time to appropriate therapy which may limit the clinical impact of treatment strategies. Furthermore, finding data comparing monotherapy and combination therapy where concomitant antibiotic exposure is minimized is unrealistic as critically ill patients frequently are treated empirically for concomitant infections with a plethora of various different antimicrobials. Some of these antibiotics, such as vancomycin, which lack individual activity against Gram-negative bacteria, have displayed synergy with the polymyxins *in vitro* due to cell wall and membrane pertubations.[97] This leads to a potential scenario where patients in a 'monotherapy' group might not truly have received a monotherapeutic regimen. Another characteristic that makes these analyses difficult to interpret is that different types of carbapenem-resistant organisms are often grouped together. The assumption is that all carbapenem-resistant organisms classified dichotomously according to MIC breakpoints are identical and will respond identically to therapy, regardless of mechanism of resistance and specific MIC value, and it is unlikely that this is case.

Furthermore, although more recent analyses have begun to examine "dose optimized" polymyxin therapy, the majority of publications to date do not describe the dosing of polymyxins or other combination agents, utilize suboptimal polymyxin doses, and/or do not clearly report renal dosing adjustments or MIC values of the polymyxins and/or other antimicrobials used in combination regimens for the pathogens . This is further complicated by the fact that the vast majority of previous combination studies used colistin, rather than polymyxin B, the latter which has a more favorable and

predictable PK profile. The majority of analyses are retrospective observational studies, which have inherent biases (such as confounding by indication) making it difficult to clearly interpret the results[116].

Finally, it is very important to consider site of infection in studies. Whereas the majority of the clinical studies with CRE evaluated BSI, the majority of the studies for carbapenem-resistant A. baumannii (CRAB), and carbapenem-resistant P. aeruginosa (CRPA) evaluated pneumonia. Polymyxins have been shown to be far less effective in murine lung infection models than in thigh infection models.[27, 28] Therefore, while the clinical data, presented below, attempt provide evidence toward the selection of polymyxin monotherapy versus polymyxin combination therapy, the inclusion of a variety of sites of infection within a given trial, makes interpretation challenging as different pharmacological considerations exist in the treatment of different infections sites.

In this section we describe the latest of published evidence from clinical studies on polymyxin monotherapy *versus* combination therapy for the three major target organisms: (1) carbapenem-resistant enterobacteriaceae (CRE), (2) carbapenem-resistant *A. baumannii* (CRAB), and (3) carbapenem-resistant *P. aeruginosa* (CRPA). We assess the evidence regarding combination therapy in two different types of scenarios. The first is when the polymyxin is combined with an agent to which the infecting pathogen is susceptible (R28, R30 and R32). The second is when the polymyxin is combined with an agent to which the pathogenlacks in vitro susceptibility (i.e. a “non-susceptible” agent) (R29, R31 and R33). We acknowledge the rigorous debate by noting the controversies surrounding polymyxin combination *vs*. monotherapy, often in the absence of RCTs.

Given the controversies regarding monotherapy vs. combination therapy for polymyxins, it is important to note the panel did not achieve unanimity on this topic, due to a variety of factors including limitations of published studies, lack of clear clinical evidence, and weighing the potential benefit-to-risk ratio of combination *vs*. monotherapy. Therefore, a decision was made for authors to vote on the recommendations R28 to R33. Some authors abstained from the vote. Based on these voting results, these guidelines provide the panel's consensus recommendations. In some cases, we labeled recommendations as "best practice recommendations", particularly in scenarios where the recommendations are in contrast to the currently published data and/or lack sufficient RCT evidence and represent the views of the majority of panel members as opposed to quality published studies.

It is important to realize that the recommendations voted upon and thus serving as guideline recommendations R28 to R33, are NOT meant to serve as guideline recommendations for the optimal treatment of carbapenem-resistant organisms, and are not recommending preferential use of polymyxin-based therapy for these organisms. Rather, the recommendations address scenarios where a clinician has already decided to use polymyxin-based therapy and is trying to decide between monotherapy or combination therapy.

XVI. Should monotherapy or combination therapy for polymyxin B or colistin be used to treat patients with CRE infections?

Recommendations

R28. We recommend that for invasive infections due to CRE, polymyxin B or colistin should be used in combination with ≥ 1 additional agent to which the pathogen displays a susceptible MIC. (Strong recommendation, Very low quality of evidence; panel vote 14-1 in favor of combination therapy)

Remark: The quality of the evidence was initially low given the observational data of the trials supporting combination therapy. The data were downgraded to very low for two major reasons. First, the results favouring combination therapy are inconsistent. Although several studies have shown a mortality benefit of combination therapy, there have been others that failed to demonstrate this benefit and more recent evidence suggests that such a benefit might be limited to severely ill patients. Second, although these combination studies included colistin as potential therapy not all of the combination regimens in these studies were colistin based making the exact role of polymyxin combination therapy difficult to tease out from other combination regimens.

R29: If a second active agent to which the pathogen displays a susceptible MIC is unavailable, we recommend that polymyxin B or colistin should be used in combination with a second and/or third non-susceptible agent (e.g. a carbapenem). Preference should be given to a non-susceptible agent with the lowest MIC relative to the respective susceptibility breakpoint. (Best practice recommendation, panel vote 11-4 in favor of combination therapy)

Evidence Summary

Perhaps the best evidence supporting polymyxin combination therapy comes from a series of retrospective observational studies evaluating outcomes of patients receiving combination or monotherapy for bloodstream infections due to carbapenemase- producing enterobacteriaceae (largely, although not exclusively, producing *K. pneumonia*e carbapenemase KPC)[117-120]. There are two important features of these analyses that warrant comment. First, combination therapy in each of the studies described in detail below is defined as agents to which the infecting pathogen are susceptible according to the MIC. Second, although the majority of the combination

regimens included a polymyxin (i.e. colistin) the multivariate models analyzing "combination therapy" also include regimens that did not include a polymyxin and therefore, in some scenarios, the direct applicability of the findings to the polymyxins remains unclear. It is also important to note that there is no adequately powered published RCT to examine whether therapy with polymyxins (polymyxin B or colistin) administered in combination with another active agent is superior to polymyxin B or colistin monotherapy against CRE infections.

The first studies that suggested a benefit with combination therapy for CRE bloodstream infections (BSI) were from Zarkotou et. al.[117] and Qureshi et. al.[118] Although limited by small numbers of patients both analyses showed dramatic associations between combination therapy and survival (infection-related mortality of 0/20 [0%] vs. 7/15 [47%], p = 0.001 and 28-day all-cause mortality of 2/15 [13%] vs. 11/19 [57%], p = 0.01, for patients receiving combination therapy vs. monotherapy, respectively), and the association of combination regimens with survival remained significant in the multivariate model published by Qureshi et al. (OR 0.07, 95% CI 0.009 - 0.71). Findings from Tumbarello et. al.[121] in 125 patients with BSI due to KPC-producing *K. pneumoniae* furthered these findings as combination therapy with colistin + meropenem + tigecycline was independently associated with survival (OR 0.11, 95% CI 0.02 - 0.69) when compared to monotherapy. These findings were further supported in an analysis by by two larger cohort studies[119, 167], one from Greece and the other from Italy, including patients with infections caused by carbapenemase-producing enterobacteriaceae where receipt of monotherapy (compared to combination therapy) was associated with an increased risk of death in the multivariate model. Of note, these two cohort studies pointed to a potential advantage of colistin–meropenem combination therapy when the meropenem MIC was 8 mg/L or less.[119] Interestingly, recent results

from the INCREMENT trial[120] which included 437 patients with BSI due to CRE, suggest that the true benefit of combination therapy might be limited to patients with a greater severity of illness. In this analysis, combination therapy was associated with lower mortality compared to monotherapy in the high-mortality-score stratum (30 (48%) of 63 *vs*. 64 (62%) of 103; adjusted HR 0·56, 95% CI 0·34–0·91), but not in the low-mortality-score stratum (17 (24%] of 72 *vs*. 21 (20%) of 105; adjusted odds ratio 1·21, 95% CI 0·56–2·56; p=0·62). It is important to note that the majority of patients included in the aforementioned studies had BSI.

Based on the available literature, we recommend that when polymyxins are employed for the management of invasive CRE infections that combination therapy including ≥ 1 additional agent with *in vitro* activity against the pathogen be administered. The rationale for this recommendation is based on the available observational evidence suggesting decreased mortality with combination therapy as well as concerns regarding emergence of polymyxin resistance when monotherapy is utilized. Of note, none of the aforementioned studies assessed the impact of combination regimens on development of polymyxin resistance and were based on older definitions of meropenem susceptibility which have now changed to a breakpoint of 2mg/L according to EUCAST/CLSI[13,14].

There is a notable lack of evidence assessing the impact of polymyxin combination therapy with a second non-susceptible agent on outcomes in patients with invasive CRE infections. Perhaps the best evidence suggesting a potential advantage of this strategy comes from a recently published randomized controlled trial comparing colistin monotherapy versus colistin + meropenem combination therapy for the management of carbapenem-resistant Gram-negative bacilli.[168] In this study only 9 patients (2%) had isolates susceptible (MICs ≤ 8 mg/L) to meropenem. Both clinical failure and 28-day mortality occurred in a lower proportion of patients with CRE receiving

the colistin + meropenem combination than colistin monotherapy (failure rates 18/39 [46]% vs. 23/34 [68%] p =0.19 and 28-day mortality of 21% vs. 35%; p =0.24), although statistical significance was not demonstrated.[168] Based on the lack of evidence clearly addressing this issue in CRE and the aforementioned concerns/limitations with monotherapy we recommend that if no second agents to which the infecting pathogen displays a susceptible MIC are available for combination therapy, that a second and/or third "non-susceptible" agent should be administered in combination with the polymyxin. Given the lack of evidence support, this is a best practice recommendation.

Future Research Needs

There is currently a second ongoing RCT comparing colistin monotherapy to colistin + meropenem combination therapy for the management of invasive infections due to carbapenem-resistant Gram-negative organisms (https://clinicaltrials.gov/ct2/show/ NCT01597973) Data from this study, should further elucidate the role of combinations in the management of CRE. Furthermore, given the potential advantages of polymyxin B over colistin, clinical data assessing the impact of polymyxin B-based combination regimens are needed. Future studies should also address the impact of infection site on the effectiveness of combination therapy.

XVII. Should monotherapy or combination therapy for polymyxin B or colistin be used to treat patients with carbapenem-resistant *A. baumannii* (CRAB)?

Recommendations

R30: We recommend that for invasive infections due to CRAB, polymyxin B or colistin should be used in combination with ≥ 1 additional agent to which the pathogen displays

a susceptible MIC (Best practice recommendation, panel vote 10-5 in favor of combination).

R31: If a second agent is not available to which the pathogen displays a susceptible MIC, we recommend that polymyxin B or colistin should be used alone as monotherapy. (Weak recommendation, moderate quality evidence; panel vote 8-7 in favor of monotherapy).

Remark: The quality of the evidence for this recommendation began as high based on the aforementioned randomized controlled trials. However, the quality of the evidence was finally graded as moderate due to the open label nature of the RCTs, the use of non-study anti-Gram-negative therapies and relatively low numbers of patients in the rifampin and fosfomycin studies. The strength of the recommendation is weak due to the dichotomy in our panel with regard to optimal management of these patients, potential bias in the studies, lack of adaptive feedback control to optimize polymyxin concentrations and dosing concerns in the rifampin trial.

Evidence Summary

Perhaps more than any other organism mentioned in these guidelines the retrospective CRAB literature surrounding combination therapy *versus* monotherapy are nearly uninterpretable due to confounding by indication, poorly described dosing, a lack of clarity regarding the timing of initial administration of therapy (and subsequently time to appropriate therapy) which are incompletely described. Additionally, there is often confusion in published literature as to whether or not patients had infection *versus* colonization as the infection site is often described "respiratory" without clear delineation of how infection was defined. Also, as previously discussed, given the complexity of

study patients and the lack of a true infection definition, the primary endpoint of mortality (all-cause, in-hospital, or 30-day) is suboptimal as there are often many competing mortality risks. In these studies, it is not always clear whether death was clearly associated with infection.

Therefore, the studies reviewed in this section are limited to the three major randomized, open label trials that compared colistin with a second non-susceptible agent including rifampin, fosfomycin, or meropenem.[122, 123, 168] It is worth mentioning that while some isolates in the rifampin and fosfomycin studies were defined as in vitro susceptibility to these agents. However, for the purposes of these guidelines, the panel considered these isolates be non-susceptible due to a lack of uniform susceptibility in the isolates included in these studies (not all isolates were defined as susceptible) and a lack of dose optimization strategies employed for these agents.[122, 123] Taken together with the insufficient clinical data to support efficacy, concerns for resistance development and the routine avoidance by clinicians for fosfomycin and rifampin monotherapy provides further rationale to why both of these agents were considered non-susceptible. There are currently no prospective randomized trials that study polymyxin combinations involving a second agent to which the infecting pathogen displays a susceptible MIC. Therefore, there are no clinical data assessing combination therapy with a polymyxin and a second in vitro active agent, and thus the best practice recommendation for using this strategy is an extrapolation from the CRE data. The three RCTs compared combination with a non-susceptible agent to monotherapy.

The first of the three open label RCTs comparing combinations with monotherapy was a prospective study by Durante-Mangoni et. al.[122] which enrolled 210 patients to randomly receive colistin or colistin + rifampin for the

treatment of life-threatening XDR *A. baumannii* infections. No colistin loading dose was administered and the maximum daily maintenance dose was low by current standards. Patients were randomly allocated (1:1) to either colistin alone, 2 million IU every 8 hours intravenously, or colistin plus rifampin 600 mg every 12 hours intravenously. The colistin MIC was ≤0.5 mg/L for all isolates at randomization. This analysis reported that the risk of death within 30 days was similar between combination therapy and monotherapy (OR = 0.88, 95% CI 0.46–1.69; P = 0.71) despite a significantly improved microbiological cure rate in patients receiving colistin + rifampin (P = 0.034).

Furthermore, no patients developed colistin-resistant isolates in either arm. This improvement in microbiological cure was consistent with another small randomized trial (n = 43) that compared colistin and colistin + rifampin, where time to microbiological clearance was reduced in the colistin + rifampin arm (3.1 vs 4.5 days; p = 0.029).[124] It is important to note that while rifampin displays potent *in vitro* synergy with polymyxins, there are many suboptimal pharmacological characteristics associated with the drug. In addition to drug interaction concerns due to induction of drug metabolism, rifampin is also associated with adverse drug events, including hepatotoxicity. A nonsignificantly higher rate of hepatotoxicity in the colistin + rifampin arm was identified in the Durante-Mangoni et al. trial (20.8% in the colistin + rifampin arm vs 11.9% in the colistin arm; p = 0.13).[122] In fact, 10 patients in the combination therapy arm had rifampin discontinued due to this adverse event. In such an open-label study, in patients receiving "monotherapy" it is difficult to avoid use of agents which might be provide a combinatorial benefit with polymyxins. As an example, ~70% of patients in the

monotherapy and combination groups received other antibiotics, including agents such as meropenem (which was prescribed more commonly in the monotherapy than combination therapy arm (15.9% *vs*. 3.9%, respectively).

In another open label, prospective, randomized trial of 94 patients with CRAB infections, subjects were randomised to receive colistin alone or colistin + fosfomycin.[123] Some patients in both groups received other antibiotics; for example, 17.0% and 8.5% of patients in the monotherapy and combination groups, respectively, received a carbapenem. No significant differences between monotherapy and combination therapy arms in infection-related (23.1% *vs*. 16.3%; p = 0.507) or all-cause mortality (57.4% *vs*. 46.8%; p = 0.41). Interestingly, microbiological cure in the first 72 h (65.7% *vs*. 78.8%; P = 0.028) and at the end of treatment (84.5% *vs*. 100%; P = 0.023) occurred more frequently in the combination arm.

Recently, Paul and colleagues published the largest RCT to date (AIDA Study) comparing colistin monotherapy with colistin (9 million IU or 300 mg CBA/day) + high dose extended infusion meropenem combination therapy for the treatment of carbapenem-resistant Gram-negative bacilli.[168] Although this study included CRE and carbapenem-resistant *P. aeruginosa*, 312/406 (77%) of the enrolled patients had CRAB. There was no significant difference in the rate of clinical failure or 28-day mortality between monotherapy and combination therapy in the entire cohort (156/198 [79%] vs. 152/208 [73%]; p =0.17 for clinical failure and 43% vs. 45%; p = 0.78 for 28-day mortality) or the subset of patients with *A. baumannii* infections (125/151 [83%] vs. 81%; p = 0.64 for clinical failure and 46% vs. 52%; p = 0.40 for mortality.) Ninety-four percent of patients in this study had either bacteremia or pneumonia with nearly an even split between the two. Importantly, there was also no significant difference between groups in the identification of colistin resistance in clinical samples by day 28 (6% for monotherapy

versus 5% for combination therapy; p = 0.77) or microbiological failure (31% for monotherapy versus 35% for combination therapy; p = 0.49.)

In summary, the data comparing monotherapy to combination therapy does not support the addition of that second non-susceptible agent. Therefore the evidence based recommendation is in support of monotherapy. There was significant debate and disagreement amongst the panel members surrounding this recommendation. Many members of the panel were concerned that even though the clinical evidence does not support combination therapy, the pharmacokinetic/pharmacodynamic limitations of the polymyxins, and the development of resistance remain great concerns. The small numbers and large percentage with pneumonia patients in the rifampin and fosfomycin studies as well as the limitations of the AIDA study (e.g. open label, the large number of patients treated for pneumonia and low Sequential Organ Failure scores) is why many panel members voted for combination therapy. However, the final vote was in favour of monotherapy.

Future Research Needs

An ongoing double-blind RCT will help to further shed light on the role of combinations in the management of Gram-negative infections including those caused by CRAB. Clinical data assessing the impact of polymyxin B-based combination regimens are needed. Future studies should also address the impact of infection site on the relative effectiveness of combination (as well as mono) therapy.

XVIII. Should monotherapy or combination therapy for polymyxin B or colistin be used to treat patients with Carbapenem-resistant *P. aeruginosa*?

Recommendations

R32. We recommend that for invasive infections polymyxin B or colistin should be used in combination with ≥ 1 additional agent to which the pathogen displays a susceptible MIC (Best practice recommendation, panel vote 14-1 in favor of combination therapy)

R33. If a second active agent is unavailable to which the pathogen displays a susceptible MIC, we recommend polymyxin B and colistin should be used in combination with a second and/or third non-susceptible agent (e.g. a carbapenem). Preference should be given to a non-susceptible agent with the lowest MIC relative to the respective susceptibility breakpoint. (Best practice recommendation, panel vote 11-4 in favor of combination therapy)

Evidence Summary

There is very little evidence assessing comparative outcomes of polymyxin monotherapy and combination therapy for MDR/XDR *P. aeruginosa* infections. The primary shortcoming of the available literature is that all of the analyses are retrospective and observational in nature and when analysed *P. aeruginosa* is often lumped together with other carbapenem-resistant pathogens. Therefore, many of the studies are difficult to interpret with regard to the independent impact of polymyxin combination therapy on *P. aeruginosa* infection. This section only includes those analyses that specifically focused on outcomes in *P. aeruginosa* infections.

In a small single-center retrospective study of 74 patients with healthcare-associated pneumonia caused by MDR *P. aeruginosa* who were treated with polymyxin B, there was no statistically significant difference in clinical cure rates between patients receiving polymyxin B plus another agent (mainly imipenem) and patients receiving polymyxin B monotherapy (14/28 [50%] *vs.* 21/46, [46%], p = 0.71).[169] In an additional retrospective single-center study of 258 patients with documented infections (mainly pneumonia) due to MDR Gram-negative organisms, 68 (26.4%) of which were caused by MDR *P. aeruginosa*, rates of clinical cure in patients with *P. aeruginosa* infection who received colistin monotherapy, colistin + meropenem, colistin + piperacillin/tazobactam, colistin + ampicillin/sulbactam, and colistin + other agents were 75.0% (9/12), 85.7% (24/28), 60% (6/10), 100% (1/1) and 64.7% (11/17), respectively.[170] In a retrospective multicenter study conducted by Samonis and colleagues, among 89 cancer patients with *P. aeruginosa* infection (mainly bacteremia), only 15 were treated with colistin (17%). Mortality occurred in 3/8 (37.5%) patients treated with colistin monotherapy and 4/7 (57.1%) patients receiving colistin plus another agent, mostly a ß-lactam (p = 0.8).[171] In a multicenter retrospective study, Rigatto and colleagues compared polymyxin B plus other agents with polymyxin B monotherapy for treating infections caused by *A. baumannii* and *P. aeruginosa* (mainly respiratory infections) in 101 critically ill patients.[172] Most infections were caused by *A. baumannii* (83, 82.2%), and only 18 (17.8%) were due to *P. aeruginosa*. Three of 18 patients with *P. aeruginosa* infections received combination therapy and all survived, while 14/15 patients treated with polymyxin B monotherapy died within 30 days (P = 0.005).[172]

Ribera and colleagues recently reported the results of a single-center retrospective cohort of 34 patients with osteoarticular infections due to MDR *P. aeruginosa*, 15 of whom (44.1%) had prosthetic joint infections and 19 (55.9%)

osteoarthritis. Patients were treated with intravenous antibiotics for 6 weeks.[173] Combination therapy (mainly colistin plus a ß-lactams) was associated with higher cure rates than monotherapy with colistin or a ß-lactam (11/15 [73.3%] *vs*. 6/19 [31.6%], respectively. p = 0.016).[173] Finally, Sorlí and colleagues conducted a single-center prospective study on 91 patients with infections caused by colistin-susceptible *P. aeruginosa* who were treated with colistin (most commonly pneumonia, followed by urinary tract infection).[174] No association was detected between receipt of monotherapy or combination therapy and either clinical failure or mortality

The small numbers, discordant results, retrospective nature of most studies, and inconsistencies regarding of other agents being included in combination regimens, precludes any definitive conclusion with regard to polymyxin combination therapy *versus* monotherapy for *P. aeruginosa*. Until further evidence becomes available the panel recommends that when polymyxins are used for the treatment of invasive infections caused by *P. aeruginosa*, that they be used in combination with ≥ 1 additional agent to which the pathogen displays susceptible MIC. The rationale for this recommendation is based on extrapolation of the available evidence for CRE and the potential risk for clinical failure or emergence of resistance when monotherapy is used. If no active agents are available, additional non-susceptible agents should be administered based on MIC value. Preference should be given to non-susceptible agents to which the pathogen demonstrates the lowest MIC respective to the breakpoint.

Future Research Needs

Any data, even observational in nature, assessing outcomes of polymyxin monotherapy and/or combination therapy for MDR/XDR *P. aeruginosa* are needed. Care should be taken by investigators to clearly describe polymyxin dosing, other

antimicrobials administered, and the degree of susceptibility of the pathogen to the agents included in the treatment regimens for a given isolate. Future studies should also address the impact of infection site on the relative effectiveness of combination therapy.

XIX. Should inhaled polymyxins be administered to patients with HAP/VAP and if so which agent is preferred?

Recommendations

R34. We recommend that for patients requiring intravenous polymyxin therapy for suspected or documented XDR Gram-negative HAP or VAP should receive adjunctive polymyxin aerosol therapy. (weak recommendation, low quality evidence).

R35. We recommend that for polymyxin aerosol therapy, either colistin or polymyxin B are appropriate (weak recommendation, very low quality evidence).

Evidence Summary

Only a single open-label RCT has been performed comparing empirical CMS aerosol to placebo aerosol.[127] Patients were randomized to receive either 4 mL of nebulized sterile normal saline or CMS equivalent to 75 mg of colistin base reconstituted in 4 mL of nebulized sterile normal saline was delivered immediately via a jet or ultrasonic nebulizer for 10 min or until the nebulized solution container was empty. [127] The regimen and duration of the systemic antibiotic(s) were chosen by the patient's responsible physician. No benefit in clinical cure or mortality with adjunctive aerosol CMS was demonstrated in this trial.[127] In contrast, a 2015 meta-analysis that did include this trial found that clinical response was improved (OR 1.57, 95% CI 1.14- 2.15) and mortality lower (OR 0.89, 95% CI 0.51-1.01) with adjunctive aerosol CMS. All analyses were imprecise and demonstrated inconsistency except for microbiologic eradication.[128]

Since this meta-analysis, only one retrospective cohort study in pediatric patients has been published which found essentially the same results for clinical response.[129]

Most of the studies included in the meta-analysis focused on MDR pathogens, mainly *Pseudomonas*, *Acinetobacter* and CRE[128, 129]. The majority had carbapenem-resistant or colistin-only susceptible isolates. In many cases, polymyxin aerosols were only added after culture results were known. As such, early effective empirical antibiotic therapy, critical for good outcomes in HAP/VAP, may have been inadequate even in those receiving polymyxin aerosols.

The assumption is that intravenous colistin may be considered in the patients with pneumonia due to XDR pathogens. Poor results with lower dose intravenous therapy and higher nephrotoxicity with high dose therapy,[130] safety concerns when combination therapy includes other nephrotoxic agents, and poor response to polymyxins in preclinical lung infection murine models all warrant consideration of polymyxin aerosols as an adjunctive therapy to intravenous polymyxins. Use of aerosolized CMS, mainly monotherapy without any intravenous therapy, for all XDR *Pseudomonas*/*Acinetobacter* VAPs had equivalent results to intravenous therapy of less resistant strains.[131] An increase in nephrotoxicity is difficult to detect in the meta-analysis[128] since all studies used intravenous colistin in addition to aerosol and used various doses of intravenous colistin but overall nephrotoxicity rates were high in most studies. These recommendation place high value on pharmacologic considerations in lieu of no comparative studies.

The overwhelming number of case-control studies and the single RCT[127] used CMS. No direct comparison of CMS and polymyxin B has been performed. Both polymyxins have been used anecdotally as there are published case series[132, 133] and

appear to have equivalent adverse events, mainly bronchospasm. Of concern is that only 9% of the CMS dose reaches the alveolar level and only 16% of that was converted from the prodrug to active colistin.[134] Colistin levels achieved in alveolar fluid at the end of an 8-hour interval may be below the MIC of MDR pathogens, raising the possibility of failure.[135] It is important to note that colistin has been shown to bind to secretory mucin in sputum or epithelial mucin that lines airways, which may reduce the antibacterial efficacy of inhaled or intravenously administered colistin.[175] Furthermore, a major concern is the actual aerosol delivery.[136] Experimental studies have demonstrated significant variation in the amount of drug deposited at the alveolar level in mechanically ventilated patients. [137] A survey found that 30% of intensivists in Europe and France have used aerosolized antibiotics at least every other month.[138] However, most did not vary ventilator settings to optimize delivery of the antibiotic to the alveolar level. Therefore, optimizing ventilator settings and aerosol generator capabilities likely played a much greater role in clinical response in studies in which polymyxin was used.

Future Research Needs

Prospective clinical trials evaluating adjunctive polymyxin aerosol therapy in addition to IV therapy are necessary. PK and PK/PD studies in lung infection employing i) aerosol therapy, ii) adjunctive aerosol therapy in combination with IV polymyxin therapy and iii) adjunctive aerosol therapy in combination with IV polymyxin together with other IV active antibiotics therapy are necessary. Comparative studies between aerosol polymyxin B and colistin are also needed.

Intrathecal (IT) and Intraventricular (IVT) administration of polymyxins

XX. Should intraventricular and intrathecal administration of polymyxins be considered in meningitis or ventriculitis?

Recommendations

R36. Intraventricular (IVT) or intrathecal (ITH) administration of polymyxins at a dosage of 125,000 IU CMS (~4.1 mg CBA) or 5 mg (50,000 IU) polymyxin B) per day with concomitant IV polymyxin is recommended for ventriculitis or meningitis caused by MDR and XDR Gram-negative pathogens.

R37. Due to limited experience with polymyxin B, CMS is the preferred polymyxin for intraventricular or intrathecal administration

Evidence Summary

Healthcare-associated ventriculitis and meningitis is an evolving occurrence due to the increasing rates of neurosurgery procedures. The most prevalent pathogens are staphylococci and MDR and XDR Gram-negatives (*A. baumannii, P. aeruginosa and K. pneumoniae*) depending on local epidemiology data.[139, 140] Therapeutic treatment has become increasingly challenging due to the increasing emergence of multi-drug resistance, and in some cases colistin or polymyxin B being the only available antimicrobial agents active against meningitis pathogens.[141] Colistin exhibits limited penetration into the cerebrospinal fluid (CSF), with only 5% of serum colistin levels being detected in the CSF after intravenous administration.[142] In the presence of meningitis an increase of CSF colistin concentrations (34 to 67% of serum colistin levels) has been reported after intravenous administration, although CSF colistin levels of only 0.5 mg/L have been reported in the setting of meningitis, suggesting potentially subtherapeutic colistin CSF concentrations following intravenous colistin administration.[143] On the other hand, IVT administration of colistin in 9 neurosurgery patients with XDR Gram-negative infections achieved an estimated average steady-state concentrations of colistin in the

CSF ranging from 3.0 mg/L to 12.2 mg/L; in the 8 patients who were administered CMS IVT at a dosage of 60,000 IU to 125,000 IU (this relates to 1.8 mg CBA to 4.1 mg CBA) per day, trough CSF levels were between 2.0 mg/L and 9.7 mg/L. [144] Thus, the measured CSF concentrations in these patients were continuously above the colistin MIC breakpoint of 2 mg/L and clearance of colistin in the CSF was dependent on the amount of CSF drained. It is clear that administration of CMS directly into the CSF achieves concentrations of colistin that could not be safely obtained with intravenous administration alone.

There is a lack of information on the CSF pharmacokinetics of polymyxin B. Superiority of combined treatment with intravenous and IVT colistin treatment with greater potential of eradication of Gram-negative bacilli from CSF has been documented with no evidence of drug accumulation over time.[145] Intraventricular polymyxin dose is diluted with 3 – 4 mL of sterile normal saline and given after removal of equal volume of CSF. After polymyxin administration, the ventricular drainage is flushed with 2 ml of saline solution to minimize the dose remaining in the drainage and given through an external ventricular drain, which is clamped for 1 hour. Intrathecal (ITH) polymyxin is administrated through a lumbar drain.[146] The recommended dose by the European Medicines Agency (EMA) and Infectious Diseases Society of America (IDSA) for IVT/ITH colistin is 125 000 IU (~4.1 mg CBA) [58,139], whereas for polymyxin B 50 000 IU for adults and 20 000 IU for children recommended by the IDSA.[139]

A systematic review of the evidence regarding clinical efficacy and safety of intraventricular or intrathecal colistin or polymyxin B was conducted.[145-162] A total of 234 cases of Gram-negative healthcare-associated ventriculitis or meningitis treated with IVT or ITH colistin or polymyxin B have been reported. IVT or ITH colistin was administered in 87% of cases and polymyxin B in the remaining 13%. In the majority of cases (90%),

IVT/ITH polymyxins were administered once daily. Monotherapy with IVT/ITH polymyxins was given in 24 cases, whereas in the remaining cases a variety of parenteral antimicrobials (including polymyxins) were also administered. The median dose of CMS administered through the IVT or ITH route was 125,000 IU (~4.1 mg CBA) per day, whereas for polymyxin B it was 50,000 IU (5 mg) per day with a mean duration of 18 days. Antimicrobial therapy was administered *via* a ventricular drain in cases of ventriculitis and clamped for 60 minutes. Successful outcomes were reported in 85% of cases: 144/167 cases (86%) caused by *A. baumannii*, 39/46 (85%) caused by *P. aeruginosa*, and 17/21 (81%) caused by *K. pneumoniae.* Toxicity was noted in 16 cases (7%), mostly presenting as chemical ventriculitis or meningitis in 2 and 9 cases, respectively. Seizures were reported in 3 cases, numbness of extremities in 2 cases and cauda equina syndrome in one.[145-147]

Future Research Needs

Any additional data, even observational in nature, assessing polymyxin intraventricular and intrathecal administration are urgently needed to improve the recommendations in this section.

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