Journal of Global Antimicrobial Resistance 1 (2013) 131–134

Contents lists available at SciVerse ScienceDirect

Journal of Global Antimicrobial Resistance

journal homepage: www.elsevier.com/locate/jgar

Global survey of polymyxin use: A call for international guidelines☆

Heiman Wertheim [a,b,*], Kinh Van Nguyen [c], Gabriel Levy Hara [d], Hellen Gelband [e], Ramanan Laxminarayan [e,f], Johan Mouton [g], Otto Cars [h]

[a] Wellcome Trust Major Overseas Program, Oxford University Clinical Research Unit, National Hospital for Tropical Diseases, Hanoi, Viet Nam
[b] Nuffield Department of Clinical Medicine, Centre for Tropical Diseases, Oxford, UK
[c] National Hospital for Tropical Diseases, Hanoi, Viet Nam
[d] Infectious Diseases Unit, Hospital Carlos G. Durand, Buenos Aires, Argentina
[e] Center for Disease Dynamics Economics and Policy, Washington, DC, USA
[f] Princeton University, Princeton, NJ, USA
[g] Department of Medical Microbiology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands
[h] Action on Antibiotic Resistance (ReAct), Department of Medical Sciences, Uppsala University, Uppsala, Sweden

ARTICLE INFO

Article history:
Received 23 December 2012
Received in revised form 20 March 2013
Accepted 25 March 2013

Keywords:
Colistin
Polymyxin
Multidrug-resistant
Use
Survey
Global

ABSTRACT

Polymyxins (polymyxin B and colistin) are older bactericidal antibiotics that are increasingly used to treat infections caused by multidrug-resistant (MDR) Gram-negative bacteria. However, dosing and clinical use of these drugs vary widely. This survey was undertaken to reveal how polymyxins are used worldwide. Data were collected through a structured online questionnaire consisting of 24 questions regarding colistin usage patterns and indications as well as colistin dosage for adult patients. The questionnaire was disseminated in 2011 to relevant experts worldwide and was completed by 284 respondents from 56 different countries. Respondents from 11/56 countries (20%) had no access to colistin; 58/284 respondents (20.4%) reported that in 2010 they experienced that colistin was not available when needed. Formulations of polymyxins used were reported as: colistimethate sodium (48.6%); colistin sulfate (14.1%); both (1.4%); polymyxin B (1.4%); and unknown. Intravenous formulations were used by 84.2%, aerosolised or nebulised colistin by 44.4% and oral colistin for selective gut decontamination by 12.7%. Common indications for intravenous colistin were ventilator-associated pneumonia, sepsis and catheter-related infections with MDR Gram-negative bacteria. Only 21.2% of respondents used a colistin-loading dose, mainly in Europe and North America. This survey reveals that the majority of respondents use colistin and a few use polymyxin B. The survey results show that colistin is commonly underdosed. Clear guidance is needed on indications, dosing and antibiotic combinations to improve clinical outcomes and delay the emergence of resistance. Colistin should be considered a last-resort drug and its use should be controlled. International guidelines are urgently needed.

1. Introduction

Severe multidrug-resistant (MDR) Gram-negative infections are increasing worldwide [1]. The emergence of carbapenem resistance in Gram-negative bacteria is of extreme concern as few therapeutic options remain [1]. For this reason, clinicians are increasingly using an older class of antibiotics, namely the polymyxins, most commonly colistin (polymyxin E) [2].

Colistin is a bactericidal antibiotic with a broad Gram-negative spectrum, consisting of a mixture of colistin A and colistin B, differing in their fatty acid side chain. The active compound was isolated from the bacterium *Bacillus polymyxa* var. *colistinus* in 1949 and was used in patients for the first time in 1959. Polymyxins have been used rarely since the 1970s when less toxic aminoglycosides and other antibiotics came on the market [3]. Polymyxins, developed over 50 years ago, have not been subjected to the rigorous studies to optimise dosing regimens and to demonstrate efficacy that are currently required by regulatory agencies for new drugs [3]. The appropriate dosing schedule for these drugs, how long they should be administered, and with which other antibiotics they should be used are questions remaining to be answered [2–5]. Insights into pharmacodynamic

* Corresponding author at: Wellcome Trust Major Overseas Program, Oxford University Clinical Research Unit, National Hospital for Tropical Diseases, Hanoi, Viet Nam.
E-mail address: Heiman.wertheim@gmail.com (H. Wertheim).

2213-7165/$ – see front matter © 2013 International Society for Chemotherapy of Infection and Cancer. Published by Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.jgar.2013.03.012

properties and dose–effect relationships have only recently be partly elucidated, but many questions still remain [6]. The lack of documented experience with the drug and the availability of various forms of polymyxins with different concentrations and even units used in different dosing schemes have also led to inappropriate use. Furthermore, access to polymyxin drugs and other 'forgotten antibiotics' is limited – even in developed nations – for economic reasons [7].

Considering that no new antibiotics covering MDR Gram-negative bacteria can be expected to reach the market in the near future, it is essential to use the polymyxin class of antibiotics optimally and rationally [8,9]. Providing early adequate therapy is critical in patients with severe infections caused by MDR bacteria [8,9]. Underdosing runs the risk of treatment failure, poor outcome and potentially the development and spread of polymyxin resistance [6]. It is currently unknown which doses clinicians use and whether they are using colistin loading doses. It is also not known with which other drugs colistin is being combined.

To assess global polymyxin availability and parenteral use practices, an online survey was conducted.

2. Methods

To assess global systemic polymyxin use, a 24-question survey (see Appendix) was developed that sought information on: characteristics of the respondents; indications for use of polymyxins; access to polymyxins and drug type; cost of polymyxins; dosing of polymyxins; adverse events; antibiotic combinations; and research needs. Topical polymyxin use was not covered in this survey.

Supplementary material related to this article found, in the online version, at doi:10.1016/j.jgar.2013.03.012.

The questionnaire was peer-reviewed by three working groups working on antibiotic resistance: (i) Global Antibiotic Resistance Partnership (GARP); (ii) Action on Antibiotic Resistance (ReAct); and (iii) the Antimicrobial Stewardship Working Group of the International Society of Chemotherapy. The final version was piloted and then made freely available through an online survey website (http://www.freeonlinesurveys.com).

Professionals (e.g. infectious diseases doctors, pharmacists, microbiologists, intensive care physicians) in relevant networks were invited by email to complete the questionnaire. All invitees were asked to forward the email to anyone they considered relevant to complete the survey. The survey was open from 1 June to 1 November 2011. Data were analysed using descriptive statistics using SPSS v.15 (SPSS Inc., Chicago, IL).

3. Results

3.1. Respondent characteristics

The survey was completed by 284 respondents from 56 different countries (Table 1 and Fig. 1). The majority of respondents were from Europe, followed by the Americas, and most worked in tertiary care teaching hospitals. Approximately one-half of the respondents worked in hospitals with more than 500 beds. Most of the hospitals had an intensive care unit (89.4%), department of surgery (92.6%) and a microbiology laboratory (91.9%). All respondents had a medical background relevant to the survey (Table 1).

Table 1
Characteristics of the respondents regarding country, hospital and profession ($N = 284$).

Characteristic	*n* (%)
World regions	
Europe	115 (40.5)
South America	64 (22.5)
North America	33 (11.6)
Oceania	35 (12.3)
Asia	26 (9.2)
Africa	11 (3.9)
Hospital type[a]	
Primary care	47 (16.5)
Secondary care	74 (26.1)
Tertiary care	205 (72.2)
Teaching	185 (65.1)
Profession	
Infectious diseases doctor	144 (50.7)
Clinical microbiologist	35 (12.3)
Intensive care doctor	50 (17.6)
Pharmacist	22 (7.7)
Other	33 (11.6)

[a] Respondents were able to select more than one possibility, therefore figures do not add to 100% (e.g. tertiary hospital and teaching are not mutually exclusive; some respondents worked at several places).

3.2. Polymyxin drug access

Respondents in 11 (20%) of 56 countries reported that they had no access to colistin at the time of the survey. Lack of access was reported from all continents except Oceania and North America. The countries for which no access was reported, included Bolivia, Guatemala, Indonesia, Laos, Norway, Portugal, Russia, Uzbekistan, Venezuela, Vietnam and Yemen (Fig. 1; data by respondent available from the corresponding author by request). The survey also asked about the consistency of supply of polymyxin drugs in the respondents' institutions. Of the 284 respondents, 58 (20.4%) reported that these drugs were unavailable for patients at least once during the preceding year (Fig. 1).

Various forms of polymyxin drugs are available and used worldwide. The majority of respondents used colistimethate sodium (48.6%), followed by colistin sulfate (14.1%), both forms of colistin (1.4%) and polymyxin B (1.4%), and the remainder did not know the exact formulation. Eighty percent of the reported colistin sulfate use originated from Europe and South America. No colistin sulfate was reported from Asia. Polymyxin B was used only in South America (Brazil and Panama) and Asia (Singapore). As Polymyxin B is rarely used, further analysis here is limited to colistin.

The number of patients [median; interquartile range (IQR)] treated with polymyxin drugs by region in the year 2010 was: 30 (IQR 100) in Africa; 32 (IQR 300) in Asia; 5 (IQR 24) in Europe; 2 (IQR 20) in North America; 2 (IQR 4) in Oceania; and 15 (IQR 30) in South America.

3.3. Indications for colistin

Colistin is administered via different routes, depending on the indication. Of the 284 respondents, 84.2% used colistin intravenously, 44.4% used aerosolised or nebulised colistin and 12.7% used oral colistin for selective gut decontamination. Common indications for intravenous colistin use were ventilator-associated pneumonia, sepsis and catheter-related infections with MDR Gram-negative bacteria. Nebulised colistin was often used in cystic fibrosis patients. Colistin was used most commonly against *Acinetobacter baumannii* and *Pseudomonas aeruginosa*. Oral colistin for selective gut decontamination was most frequently reported from Europe, followed by North America. No African respondents reported oral colistin use.

3.4. Dosing of colistin

The dosing schedule for an adult patient with a weight of 70 kg and normal renal function (the standard case posed in the questionnaire) varied considerably, partly reflecting the different types of formulations. Dosing data were reported in million