Clinical Microbiology and Infection xxx (2018) 1–7

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Original article

Antibiotic treatment of infections caused by carbapenem-resistant Gram-negative bacilli: an international ESCMID cross-sectional survey among infectious diseases specialists practicing in large hospitals

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ARTICLE INFO

Article history:
Received 25 October 2017
Received in revised form
12 January 2018
Accepted 17 January 2018
Available online xxx

Editor: A. Huttner

Keywords:
Acinetobacter baumannii
Carbapenem
Carbapenem-resistant Gram-negative bacilli
Combination therapy
Enterobacteriaceae
Polymyxin
Pseudomonas aeruginosa
Survey

ABSTRACT

Objectives: To explore contemporary antibiotic management of infections caused by carbapenem-resistant Gram-negative bacteria in hospitals.
Methods: Cross-sectional, internet-based questionnaire survey. We contacted representatives of all hospitals with more than 800 acute-care hospital beds in France, Greece, Israel, Italy, Kosovo, Slovenia, Spain and selected hospitals in the USA. We asked respondents to describe the most common actual practice at their hospital regarding management of carbapenem-resistant *Enterobacteriaceae*, *Acinetobacter baumannii* and *Pseudomonas aeruginosa* through close-ended questions.
Results: Between January and June 2017, 115 of 141 eligible hospitals participated (overall response rate 81.6%, country-specific rates 66.7%–100%). Most were tertiary-care (99/114, 86.8%), university-affiliated (110/115, 89.1%) hospitals and most representatives were infectious disease specialists (99/115, 86.1%). Combination therapy was prescribed in 114/115 (99.1%) hospitals at least occasionally. Respondents were more likely to consider combination therapy when treating bacteraemia, pneumonia and central nervous system infections and for *Enterobacteriaceae*, *P. aeruginosa* and *A. baumannii* similarly. Combination of a polymyxin with a carbapenem was used in most cases, whereas combinations of a polymyxin with tigecycline, an aminoglycoside, fosfomycin or rifampicin were also common. Monotherapy was used for treatment of complicated urinary tract infections, usually with an aminoglycoside or a polymyxin. The intended goal of combination therapy was to improve the effectiveness of the treatment and to prevent development of resistance. In general, respondents shared the misconception that combination therapy is supported by strong scientific evidence.

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https://doi.org/10.1016/j.cmi.2018.01.015

Conclusions: Combination therapy was the preferred treatment strategy for infections caused by carbapenem-resistant Gram-negative bacteria among hospital representatives, even though high-quality evidence for carbapenem-based combination therapy is lacking. **L. Papst, Clin Microbiol Infect 2018;▪:1**

Introduction

Treatment of infections caused by carbapenem-resistant Gram-negative bacilli (CRGNB) represents a difficult challenge for physicians because of the paucity of antibiotics active against these bacteria and potential inferior efficacy of the old drugs [1]. Mortality rates are high and despite increasing incidence of these infections worldwide there is no consensus on the most appropriate treatment strategy due to lack of high-quality evidence from randomized controlled trials (RCTs) [1,2].

In vitro studies suggest synergistic interactions between several antibiotic combinations against CRGNBs. Combinations that have shown synergy include colistin and rifampicin [3–5], carbapenem and sulbactam [4], polymyxin and a carbapenem [6,7], tigecycline and colistin [8], carbapenem and an aminoglycoside [9] and double carbapenem combinations [10,11]. Interactions are dependent on bacterial species (*Enterobacteriaceae*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*), the inoculum and the mechanisms of resistance [7].

Following these *in vitro* data, observational studies in the last decade suggested that combination therapy with two or more agents was associated with better outcomes compared with monotherapy with an active antibiotic [12–15], at least in patients with a high risk of death [16]. Unlike the *in vitro* studies, the observational studies commonly do not address defined antibiotic combinations [13]. Evaluating effectiveness from these studies is complicated due to difficulties in avoiding selection bias, addressing confounding and assigning the treatment groups, as well as poor adherence to the assigned regimen in clinical practice [17,18].

The aim of our cross-sectional questionnaire survey was to explore how hospital infection specialists manage infections caused by CRGNB in selected European countries, Israel and selected hospitals in the USA. We wished to record the most common antibiotic practices along with factors that influenced the decision on antibiotic choice.

Materials and methods

Survey design

The study was a cross-sectional internet-based questionnaire survey on therapy for infections caused by CRGNB. The questionnaire was designed with closed-ended questions and distributed using the SurveyMonkey® platform [19]. We requested information on the specialty of the participant, hospital name, and size and type of hospital. Questions on monotherapy, double combination and triple combination therapy of infections caused by different carbapenem-resistant bacteria followed [20]. Finally, the use of carbapenems, polymyxins and tigecycline was investigated (the full questionnaire is available in the Supplementary material). The questionnaire was developed by two primary investigators (LP, MP) and pre-tested by all authors for clarity and technical functionality.

Our target population comprised infectious diseases (ID), clinical microbiology (CM) physicians or pharmacists treating patients, giving advice on antibiotic treatment or the professionals responsible for the antimicrobial stewardship programme. We asked respondents to reply describing the most common actual practice at their hospital. Only one participant from a particular hospital was included. In Europe and Israel we included all hospitals with more than 800 acute-care hospital beds (medicine/surgery/obstetrics) in countries reporting a high prevalence of CRGNB: France, Greece, Israel, Italy, Kosovo, Slovenia and Spain. In the USA, we selected hospitals where at least ten patients per year were treated with polymyxins, based on surveys performed by KK for clinical studies (Florida, Georgia, Illinois, Maryland, Michigan, New York, Pennsylvania, South Carolina).

Survey administration

One investigator per country provided the list of all eligible hospitals in the selected European countries, Israel and the USA. One senior specialist (starting with the head of the infectious diseases/clinical microbiology service or pharmacist specialized in infectious diseases and antimicrobial stewardship) per hospital was sent an invitation by the survey coordinator and the national contact via email. If a response was not obtained we searched for another contact person. Participants were able to access the questionnaire multiple times to allow for possible changes and completion at later times.

The survey was voluntary, with no incentives offered to participants (other than being listed as an investigator).

Response rates

The unit measured with regards to the survey responses was the hospital. Response rates were calculated as number of hospitals from which an answer was recorded/total number of participating hospitals, overall and per country. Information on hospital name and country was used to screen for duplicate entries, but all data were subsequently anonymized for the analyses.

Statistical analysis

Both completed and partially completed questionnaires were analysed using the number of completed responses per item as the denominator.

Results

The survey was administered between January and June 2017. A total of 115 of 141 invited hospitals participated in the study (overall response rate 81.6%, country-specific rates 66.7%–100%) (see Supplementary material, Table S1). The vast majority of respondents were ID specialists (99/115, 86.1%). Most participating centres were tertiary care (99/114, 86.8%) and university-affiliated (110/115, 89.1%) hospitals (see Supplementary material, Table S2).

Please cite this article in press as: Papst L, et al., Antibiotic treatment of infections caused by carbapenem-resistant Gram-negative bacilli: an international ESCMID cross-sectional survey among infectious diseases specialists practicing in large hospitals, Clinical Microbiology and Infection (2018), https://doi.org/10.1016/j.cmi.2018.01.015