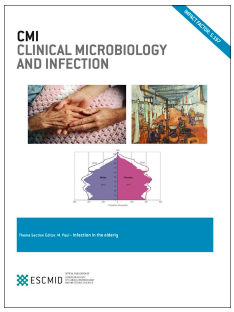
Accepted Manuscript



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

Lea Papst, Bojana Beović, Céline Pulcini, Emanuele Durante-Mangoni, Jesús Rodríguez-Baño, Keith S. Kaye, George L. Daikos, Lul Raka, Mical Paul, collab-au on behalf of ESGAP, ESGBIS, ESGIE and the CRGNB treatment survey study group

PII: S1198-743X(18)30069-7

DOI: 10.1016/j.cmi.2018.01.015

Reference: CMI 1185

To appear in: *Clinical Microbiology and Infection*

Received Date: 25 October 2017

Revised Date: 12 January 2018

Accepted Date: 17 January 2018

Please cite this article as: Papst L, Beović B, Pulcini C, Durante-Mangoni E, Rodríguez-Baño J, Kaye KS, Daikos GL, Raka L, Paul M, collab-au on behalf of ESGAP, ESGBIS, ESGIE and the CRGNB treatment survey study group Antibiotic treatment of infections caused by carbapenem-resistant Gram-negative bacilli: an international ESCMID cross-sectional survey among infection diseases specialists practicing in large hospitals, *Clinical Microbiology and Infection* (2018), doi: 10.1016/j.cmi.2018.01.015.

Original article

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

Lea Papst[1*], Bojana Beović[1,2], Céline Pulcini[3,4], Emanuele Durante-Mangoni[5,6], Jesús Rodríguez-Baño[7], Keith S Kaye[8], George L Daikos[9], Lul Raka[10,11], Mical Paul[12,13] on behalf of ESGAP, ESGBIS, ESGIE and the CRGNB treatment survey study group

[1] Department of Infectious Diseases, University Medical Centre Ljubljana, Slovenia

[2] Faculty of Medicine, University of Ljubljana, Slovenia

[3] Université de Lorraine, EA 4360 APEMAC, Nancy, France

[4] CHRU de Nancy, Service de Maladies Infectieuses et Tropicales, Nancy, France

[5] Department of Internal Medicine, University of Campania "Luigi Vanvitelli", Italy

[6] Unit of Infectious and Transplant Medicine, AORN dei Colli-Monaldi Hospital, Naples, Italy

[7] Unidad Clínica de Enfermedades Infecciosas y Microbiología, Hospital Universitario Virgen Macarena/Departamento de Medicina, Universidad de Sevilla/Instituto de Biomedicina de Sevilla (IBiS), Seville, Spain

[8] Department of Internal Medicine, Division of Infectious Diseases, University of Michigan Medical School, Ann Arbor, Michigan, USA

[9] National and Kapodistrian University of Athens, Laikon General Hospital, Athens, Greece

[10] National Institute of Public Health of Kosova, Prishtina, Kosovo

[11] Medical Faculty, University of Prishtina, Kosovo

[12] Infectious Diseases Institute, Rambam Health Care Campus, Haifa, Israel

[13] Ruth and Bruce Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel

*Corresponding author. Department of Infectious Diseases, University Medical Centre Ljubljana, Japljeva 2, 1525 Ljubljana, Slovenia. E-mail: lea_papst@yahoo.com; Tel: +38615222110; Fax: +38615222456

Running title: International survey on treatment of CRGNB infections

Abstract

Objectives: To explore contemporary antibiotic management of infections caused by carbapenem-resistant Gram-negative bacteria (CRGNB) 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 United States. 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-June 2017, 115/141 of 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 bacteremia, 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, while 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 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.

Conclusions: Combination therapy was the preferred treatment strategy for infections caused by CRGNB among hospital representatives, even though high-quality evidence for carbapenem-based combination therapy is lacking.

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 randomised 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] among others. Interactions are dependent on bacteria 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 to 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 difficult due to difficulties in avoiding selection bias, addressing confounding, 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 United States of America (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 File). The questionnaire was developed by two primary investigators (LP, MP) and pre-tested by all authors for clarity and technical functionality.

Our target population were infectious diseases (ID), clinical microbiology (CM) physicians or pharmacists treating patients, giving advice on antibiotic treatment or the professionals responsible for antimicrobial stewardship programme (ASP). 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 10 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 ID/CM service or pharmacist specialised 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 anonymised 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-June 2017. One hundred and fifteen out of 141 invited hospitals participated in the study (overall response rate 81.6%, country-specific rates 66.7%-100%) (Supplementary File, Table S1). The vast majority of respondents were ID specialists (99/115, 86.1%). Most participating centers were tertiary care (99/114, 86.8%) and university affiliated hospitals (110/115, 89.1%) (Supplementary File, Table S2).

Factors influencing antibiotic choice

Almost half of the respondents (54/111, 48.6%) reported having no guidelines regarding the treatment of infections caused by CRGNB, with the remainder having local guidelines (19.8%), national guidelines (18.9%) or both (12.6%). Source of infection, severity of the disease and the pathogen minimum inhibitory concentration (MIC) for the antibiotic were most frequently regarded as very important factors when choosing the antibiotic regimen for the treatment of infections caused by CRGNB (Table 1). The type of isolated microorganism and pharmacokinetic/pharmacodynamic profile of the antibiotic were also considered as important, while a patient's immune status was a lesser determinant of treatment choice.

Antibiotics used

The polymyxin used in almost all participating hospitals was colistin, most frequently dosed twice daily following a 9 million international units (MIU) loading dose (Table 2). Therapeutic drug monitoring for polymyxins was routinely used in 5/112 (4.5%) hospitals and was available for specific indications (e.g. renal failure) in 13/112 (11.6%) hospitals. The use of aerosolised polymyxin was frequent for ventilator-associated pneumonia (86/112, 76.8%). In more than half of hospitals, tigecycline was used in higher doses than approved: 200 mg daily in 54.5% (60/110) and 150 mg daily in 6.4% (7/110) of the hospitals. When included in combination therapy, the most common carbapenem used was meropenem (100/109, 91.7%) and prolonged infusions of carbapenems were

commonly used (Table 3). When asked about a MIC threshold for carbapenem use for CRGNBs, most respondents considered using a carbapenem-containing combination when the carbapenem MIC was ≤ 8 mg/L.

Combination therapy

Combination therapy was prescribed at least sometimes in 114/115 (99.1%) hospitals. Respondents were more likely to consider combination therapy when treating bacteremia, pneumonia and central nervous system infections and for *Enterobactericeae*, *P. aeruginosa* and *A. baumannii* similarly (Table 4). When asked on what basis the decision to use combination rather than monotherapy was based on, 63/110 (57.3%) declared they relied on *in vitro* studies, 69.1% relied on observational studies, 55.5% on RCTs, 68.2% on systematic reviews and 53.6% on personal experience. The intended goal of combination therapy was most commonly to improve effectiveness of the treatment (103/110, 93.6%) or to prevent development of resistance (73.6%). Less commonly combination therapy was used to avoid toxicity through dose reduction (5.5%).

Carbapenem-resistant Enterobacteriaceae

Treatment strategies for infections caused by carbapenem-resistant *Enterobacteriaceae* (CRE) are presented in Table 5. The mechanisms of carbapenem resistance reported by respondents as most frequent in their practice were production of *Klebsiella pneumoniae* carbapenemase (KPC) (64%) and oxacillinase-48 (OXA-48) (47.4%) (Supplementary File, Table S3). Combination therapy was a common strategy for treatment of CRE. When monotherapy was considered, aminoglycosides (40/57, 70.2%) or ceftazidime/avibactam (20/57, 35.1%) were used for complicated urinary tract infections (cUTIs) and tigecycline was used especially for intraabdominal infections (IAIs) (20/57, 35.1%) and skin and soft tissue infections (SSTIs) (20/57, 35.1%). The most popular choices for double combination therapy were combinations of a polymyxin with a carbapenem (e.g. for treating bacteremia in 63.9% (67/105) of hospitals) followed by a polymyxin with tigecycline (e.g. for treating IAIs in 58.1% (61/105) of hospitals). For treatment of IAIs and SSTIs combinations of tigecycline with either a

carbapenem or an aminogycoside were common and the combination of an aminoglycoside with fosfomycin (34/105, 32.4%) was often used for cUTIs. For triple combination therapy, a regimen containing a polymyxin, tigecycline and either a carbapenem (e.g. for treating bacteremia in 55.6% (40/72) of hospitals) or an aminogycoside (e.g. for treating bacteremia in 29.2% (21/72) of hospitals) was often used in participating hospitals.

Extensively drug-resistant carbapenem-resistant P. aeruginosa

Antibiotic choices for treatment of infections caused by extensively drug-resistant carbapenem-resistant *P.aeruginosa* (XDR CRPa) are shown in Table 6. Monotherapy was used mostly for cUTIs and ceftolozane/tazobactam (41/66, 62.1%) was the preferred option, followed by aminoglycosides (32/66, 48.5%) or polymyxins (23/66, 34.8%). When treating with combination, a polymyxin was usually used as a backbone with a carbapenem (e.g. for treating bacteremia in 54.7% (52/95) of hospitals), an aminoglycoside or fosfomycin added to it. For triple combination therapy a polymyxin and a carbapenem were usually combined with either fosfomycin or an aminoglycoside.

Extensively drug-resistant carbapenem-resistant A. baumannii

Treatment options for infections caused by extensively drug-resistant carbapenem-resistant *A. baumannii* (XDR CRAb) are presented in Table 7. Monotherapy was used in 46/96 (47.9%) hospitals and mainly for cUTI. Aminoglycosides (29/46, 63%) and polymyxins (30/46, 65.2%) were the main treatment for cUTI and polymyxins for various different infections. Most respondents used double combination therapy for infections caused by CRAb. Combinations of a polymyxin with a carbapenem (e.g. for treating bacteremia in 60% (48/80) of hospitals) were most frequently followed by a polymyxin combined with either tigecycline or rifampin. Triple combination therapy was as commonly used as monotherapy; a polymyxin plus tigecycline with a carbapenem or rifampicin were the preferred choices.

Differences between participating countries

Israel was the only country where monotherapy was the preferred choice of treatment for infections caused by CRGNB, in all other countries combination therapy, usually the association of two antibiotics was the standard of care. However, monotherapy for cUTI was also very common in Kosovo, Slovenia, Spain and the USA. There were no major differences in the selection of antibiotics most commonly used, but some distinctions between countries were noted. Ceftolozane/tazobactam was commonly used for treatment of cUTI and pneumonia caused by XDR CRPa in France, Italy, Spain and the USA, while ceftazidime/avibactam was used often for treatment of infections caused by CRE in the USA. Polymyxin B was used only in some hospitals in the USA, all other hospitals used colistin. These differences were dictated by availability, as ceftolozane/tazobactam, ceftazidime/avibactam, polymyxin B and intravenous fosfomycin were not available in all countries at the time of the survey. Country level data are presented in detail in Supplementary File, Tables S7-S14.

Discussion

The aim of our survey was to explore treatment regimens for infections caused by CRGNB used by hospital infection specialists in various countries. Our results show that source of infection, severity of the disease and the MIC for the antibiotic were the most important factors influencing the antibiotic choice. Double combination therapy was the preferred strategy for CRGNB infections, especially when treating bacteremia, pneumonia and central nervous system infections. Combination of a polymyxin with a carbapenem was used in most cases, while combinations of a polymyxin with tigecycline, an aminoglycoside, fosfomycin or rifampicin were also common. Monotherapy was mainly used for treatment of cUTIs, usually with an aminoglycoside or a polymyxin. Ceftazidime/avibactam, approved by the US Food and Drug Administration at the time of the survey but not yet by the European Medical Association, was often used for monotherapy of infections caused by CRE in USA, while ceftolozane/tazobactam was used for monotherapy of infections caused by CRPa in all countries except Israel. Among polymyxins, colistin was almost universally used, mostly dosed twice daily after the initial 9 MIU loading dose. In more than 10% of the hospitals a loading dose was not used. Participants felt comfortable adding a carbapenem when the MIC was ≤ 8 mg/L, and carbapenems were commonly administered in prolonged infusions. Tigecycline was generally used for treating IAIs and SSTIs, often in higher than approved doses.

In general, respondents shared the misconception that combination therapy is supported by strong scietific evidence (i.e. randomised-controlled trials). In fact, there were three RCTs published at the time of the survey that tested only two interventions, only for *A. baumannii* – colistin-rifampicin vs. colistin [21,22] and colistin-fosfomycin vs. colistin [23]. There were no published RCTs on carbapenem-combination therapy for CRGNBs (two underway at the the time of the survey, NCT01732250, NCT01597973). Many participants relied on systematic reviews; systematic reviews of observational studies do not necessarily provide better evidence than the included studies. A recent

systematic review graded the quality of the evidence on combination therapy for CRGNBs as very low quality, data that should not be used in guideline development or to support a recommendation [18].

Clinical studies do not always mirror the results of *in vitro* studies [24]. Exact bacterial inoculum and antibiotic doses can be easily simultaneously assessed on agar plates but this may not be replicated in a septic patient. Even if combination therapy were to be timed perfectly, drug peneration to the site of infection cannot be controlled. Despite many *in vitro* studies demonstrating synergistic interactions and prevention of resistant strain emergence for beta-lactam-aminoglycoside combination therapy against Gram-negative bacteria, clinical studies failed to prove clinical benefits and there is no clinical demonstration of less resistance with the combination [25-28]. Indeed, the only RCTs to date of combination therapy for CRGNBs did not demonstrate reduced mortality or clinical failure with combination [21-23].

Carbapenems, mainly meropenem, were the most common antibiotics added to polymyxins in combination therapy regimens. Carbapenems are among antibiotics most commonly associated with *Clostridium difficile* diarrhoea [29]. An even graver consequence of carbapenem treatment is induction of carbapenem resistance and selection of carbapenem-resistant strains. Studies show that carbapenem use is one of the most important risk factors for colonisation and infection with CRGNB [30]. With carbapenem use as one of the main drivers of carbapenem resistance its routine use as part of the combination therapy for CRGNB infections in the absence of good quality data remains questionable.

The strength of this survey is a high response rate, giving an insight into everyday practices of infection specialists dealing with CRGNB infections in participating countries. We restricted inclusion to large hospitals in Europe, since these hospitals are more likely to care for patients with severe CRGNB infections. The main limitation is that we did not access actual antibiotic prescription data, but relied on a hospital representative. Responses might reflect personal opinion of participants on

245 treatment strategies. However, we made it clear in the online survey and in correspondence with
246 respondents that the survey intended to reflect actual common practice at the participating hospital.

247 In conclusion, combination therapy is the preferred treatment strategy for infections caused by
248 CRGNB even though high-quality evidence (supporting or not supporting this approach) are lacking.
249 The absence of good quality studies, guidelines and recommendations resulted in a myriad of
250 combination antibiotic regimens recorded in the survey. In the era of ever-growing carbapenem
251 resistance good quality studies, especially RCTs, are urgently needed to ascertain the most effective
252 treatment strategies regarding CRGNB infections. Evidence-based ESCMID guidelines on the
253 treatment of infections caused by multidrug-resistant Gram-negative bacilli are to be published in
254 2018 and might help standardise the management of CRGNBs.

Funding

Part of this work was funded by the EU-project AIDA (grant Health-F3-2011-278348) to MP, EDM, GLD and by ESCMID Mentorship Programme (LP).

Transparency declaration

EDM received funding by NIH for project HHSN272201000039C.

JRB received funding for research from Plan Nacional de I+D+i 2013-2016 and Instituto de Salud Carlos III, Subdirección General de Redes y Centros de Investigación Cooperativa, Ministerio de Economía, Industria y Competitividad, Spanish Network for Research in Infectious Diseases (REIPI RD16/0016/0001) - co-financed by European Development Regional Fund “A way to achieve Europe”, Operative Programme Intelligent Growth 2014-2020.

Other authors report no potential conflict of interest.

Acknowledgments

Members and participating centers of the CRGNB survey study group: Abbo L (Jackson Memorial Hospital, Miami, Florida, United States of America), Abgueguen P (CHU Angers, Angers, France), Almirante B (Hospital Universitari Vall d'Hebrón, Barcelona, Spain), Azzini AM (University of Verona, Verona, Italy), Bani-Sadr F (CHU Reims, Reims, France), Bassetti M (Santa Maria della Misericordia University Hospital, Udine, Italy), Ben-Ami R (Tel Aviv Medical Center, Tel Aviv, Israel), Beović B (University Medical Centre Ljubljana, Ljubljana, Slovenia), Béraud G (CHU Poitiers, Poitiers, France), Botelho-Nevers E (CHU Saint-Étienne, Saint-Étienne, France), Bou G (Hospital Universitario A Coruña, La Coruña, Spain), Boutoille D (CHU Nantes, Nantes, France), Cabié A (CHU de Martinique, Fort-de-France, France), Cacopardo B (AO Garibaldi, Catania, Italy), Cascio A (AOUP "P. Giaccone", University of Palermo, Palermo, Italy), Cassir N (CHU Marseille, Marseille, France), Castelli F (ASST Spedali Civili di Brescia, Brescia, Italy), Cecala M (ARNAS Civico Palermo, Palermo, Italy), Charmillon A (CHRU Nancy, Nancy, France), Chirouze C (CHRU Besançon, Besançon, France), Cisneros JM (Hospital Universitario Virgen del Rocío, Seville, Spain), Colmenero JD (Hospital Regional Universitario de Málaga, Málaga, Spain), Coppola N (University of Campania, Naples, Italy), Corcione S (Department of Medical Sciences, Infectious Diseases, University of Turin, Italy), Daikos GL (General University Hospital of Athens "Laiko", Athens, Greece), Dalla Gasperina D (University of Insubria, Varese, Italy), De la Calle Cabrera C (Hospital Clinic de Barcelona, Barcelona, Spain), Delobel P (CHU Toulouse, Toulouse, France), Di Caprio D (AORN Sant'Anna e San Sebastiano, Caserta, Italy), Durante Mangoni E (AORN dei Colli, Ospedale Monaldi, Naples, Italy), Dupon M (CHU Bordeaux, Bordeaux, France), Ettahar N (CH Valenciennes, Valenciennes, France), Falagas ME (Henry Dunant Hospital Center, Athens, Greece), Falcone M (Sapienza University of Rome, Rome, Italy), Fariñas MC (Hospital Universitario Marqués de Valdecilla, Santander, Spain), Faure E (CHRU Lille, Lille, France), Forestier E (CH Métropole Savoie, Chambéry, France), Foti G (Ospedale di Reggio Calabria, Reggio Calabria, Italy), Gallagher J (Temple University Hospital, Philadelphia, Pennsylvania, United States of America), Gattuso G (C. Poma Hospital, Mantova, Italy), Gendrin V (CH Belfort, Belfort, France), Gentile I

(University of Naples "Federico II", Naples, Italy), Giacobbe DR (IRCCS AOU San Martino-IST, Genoa, Italy), Gogos CA (University of Patras, Patras, Greece), Grandiere Perez L (CH Le Mans, Le Mans, France), Hansmann Y (CHU Strasbourg, Strasbourg, France), Horcajada JP (Hospital del Mar, Barcelona, Spain), Iacobello C (Azienda Ospedaliera "Cannizzaro", Catania, Italy), Jacob JT (Emory University School of Medicine, Atlanta, Georgia, United States of America), Justo JA (University of South Carolina, Columbia, South Carolina, United States of America), Kernéis S (Hôpital Cochin, Paris, France), Komnos A (General Hospital of Larissa, Larissa, Greece), Kotnik Kevorkijan B (University Medical Centre Maribor, Maribor, Slovenia), Lebeaux D (HEGP Paris, Paris, France), Le Berre R (CHRU Brest, Brest, France), Lechiche C (CHU Nîmes, Nîmes, France), Le Moing V (CHU Montpellier, Montpellier, France), Lescure FX (Hôpital Bichat, Paris, France), Libanore M (Department of Infectious Diseases, Sant'Anna Hospital and University, Ferrara, Italy), Martinot M (CH Colmar, Colmar, France), Merino de Lucas E (Hospital General Universitario de Alicante, Alicante, Spain), Mondain V (CHU Nice, Nice, France), Mondello P (AOU Policlinico "G. Martino", Messina, Italy), Montejo M (Hospital Universitario de Cruces, Bilbao, Spain), Mootien J (CH Mulhouse, Mulhouse, France), Muñoz P (Hospital General Universitario Gregorio Marañón, Madrid, Spain), Nir-Paz R (Hadassah-Hebrew University Medical Center, Jerusalem, Israel), Pan A (ASST di Cremona, Cremona, Italy), Paño-Pardo JR (Hospital Clínico Universitario “Lozano Blesa", Zaragoza, Spain), Patel G (Mount Sinai Hospital, New York, New York, United States of America), Paul M (Rambam Health Care Campus, Haifa, Israel), Pérez Rodríguez MT (Hospital de Vigo, Vigo, Spain), Piroth L (CHU Dijon, Dijon, France), Pogue J (Detroit Medical Center, Detroit, Michigan, United States of America), Potoski BA (UPMC Presbyterian, Pittsburgh, Pennsylvania, United States of America), Pourcher V (Pitié-Salpêtrière Hospital, Paris, France), Pyrpasopoulou A (Hippokration Hospital, Thessaloniki, Greece), Rahav G (Sheba Medical Center, Ramat Gan, Israel), Rizzi M (ASST Papa Giovanni XXIII, Bergamo, Italy), Rodríguez-Baño J (Hospital Universitario Virgen Macarena, Seville, Spain), Salavert M (Hospital La Fé, Valencia, Spain), Scheetz M (Northwestern Hospital, Chicago, Illinois, United States of America), Sims M (Beaumont Hospital, Royal Oak, Michigan, United States of America), Spahija G (University Clinical

Centre of Kosovo, Prishtina, Kosovo), Stefani S (University of Catania, Catania, Italy), Stefos A (University Hospital of Larissa, Larissa, Greece), Tamma PD (Johns Hopkins University School of Medicine, Baltimore, Maryland, United States of America), Tattevin P (Pontchaillou University Hospital, Rennes, France), Tedesco A (Hospital of San Bonifacio, Verona, Italy), Torre-Cisneros J (Maimonides Biomedical Research Institute of Cordoba (IMIBIC), Reina Sofia University Hospital, University of Cordoba, Cordoba, Spain), Tripolitsioti P (Agioi Anargiroi Hospital, Athens, Greece), Tsiodras S (University Hospital Attikon, Athens, Greece), Uomo G (Cardarelli Hospital, Naples, Italy), Verdon R (CHU Caen, Caen, France), Viale P (University of Bologna, Bologna, Italy), Vitrat V (CH Annecy Genevois, Annecy, France), Weinberger M (Assah Harofeh Medical Center, Zerifin, Israel), Wiener-Well Y (Shaare Zedek Medical Center, Jerusalem, Israel).

References

[1] Nabarro LEB, Veeraraghavan B. Combination therapy for carbapenem-resistant *Enterobacteriaceae*: increasing evidence, unanswered questions, potential solutions. Eur J Clin Microbiol Infect Dis 2015;34:2307-11.

[2] Tzouvelekis LS, Markogiannakis A, Piperaki E, Souli M, Daikos GL. Treating infections caused by carbapenemase-producing *Enterobacteriaceae*. Clin Microbiol Infect 2014;20:862-72.

[3] Lagerbäck P, Khine WWT, Giske CG, Tängdén T. Evaluation of antibacterial activities of colistin, rifampicin and meropenem combinations against NDM-1-producing *Klebsiella pneumoniae* in 24 h *in vitro* time-kill experiments. J Antimicrob Chemother 2016;71:2321-5.

[4] Song JY, Kee SY, Hwang IS, Seo YB, Jeong HW, Kim WJ, et al. *In vitro* activities of carbapenem/sulbactam combination, colistin, colistin/rifampicin combination and tigecycline against carbapenem-resistant *Acinetobacter baumannii*. J Antimicrob Chemother 2007;60:317-22.

[5] Tascini C, Tagliaferri E, Giani T, Leonildi A, Flammini S, Casini B, et al. Synergistic activity of colistin plus rifampin against colistin-resistant KPC-producing *Klebsiella pneumoniae*. Antimicrob Agents Chemother 2013;57:3990-3.

[6] Deris ZZ, Yu HH, Davis K, Soon RL, Jacob J, Ku CK, et al. The combination of colistin and doripenem is synergistic against *Klebsiella pneumoniae* at multiple inocula and supresses colistin resistance in an *in vitro* pharmacokinetic/pharmacodynamic model. Antimicrob Agents Chemother 2012;56:5103-12.

[7] Zusman O, Avni T, Leibovici L, Adler A, Friberg L, Stergiopoulou T, et al. Systematic review and meta-analysis of *in vitro* synergy of polymyxins and carbapenems. Antimicrob Agents Chemother 2013;57:5104-11.

[8] Pournaras S, Vrioni G, Neou E, Dendrinos J, Dimitroulia E, Poulou A, et al. Activity of tigecycline alone and in combination with colistin and meropenem against *Klebsiella*

pneumoniae carbapenemase (KPC)-producing *Enterobacteriaceae* strains by time-kill assay. Int J Antimicrob Agents 2011;27:244-7.

[9] Yadav R, Landersdorfer CB, Nation RL, Boyce JD, Bulitta JB. Novel approach to optimize synergistic carbapenem-aminoglycoside combinations against carbapenem-resistant *Acinetobacter baumannii*. Antimicrob Agents Chemother 2015;59:2286-98.

[10] Bulik CC, Nicolau DP. Double-carbapenem therapy for carbapenemase-producing *Klebsiella pneumoniae*. Antimicrob Agents Chemother 2011;55:3002-4.

[11] Oliva A, Gizzi F, Mascellino MT, Cipolla A, D'Abramo A, D'Agostino C, et al. Bactericidal and synergistic activity of double-carbapenem regimen for infections caused by carbapenemase-producing *Klebsiella pneumoniae*. Clin Microb Infect 2016;22:147-53.

[12] Petrosillo N, Giannella M, Antonelli M, Antonini M, Barsic B, Belancic L, et al. Clinical experience of colistin-glycopeptide combination in critically ill patients infected with Gram-negative bacteria. Antimicrob Agents Chemother 2014;58:851-8.

[13] Falagas ME, Rafailidis PI, Ioannidou E, Alexiou VG, Matthaiou DK, Karageorgopoulos DE, et al. Colistin therapy for microbiologically documented multidrug-resistant Gram-negative bacterial infections: a retrospective cohort study of 258 patients. Int J Antimicrob Agents 2010;35:194-4.

[14] Zarkotou O, Pournaras S, Tselioti P, Dragoumanos V, Pitiriga V, Ranellou K, et al. Predictors of mortality in patients with bloodstream infections caused by KPC-producing *Klebsiella pneumoniae* and impact of appropriate antimicrobial treatment. Clin Microbiol Infect 2011;17:1798-1803.

[15] Tumbarello M, Viale P, Viscoli C, Trecarichi EM, Tumietto F, Marchese A, et al. Predictors of mortality in bloodstream infections caused by *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae*: importance of combination therapy. Clin Infect Dis 2012;55:943-50.

[16] Gutiérrez-Gutiérrez B, Salamanca E, de Cueto M, Hsueh PR, Viale P, Paño-Pardo, et al. Effect of appropriate combination therapy on mortality of patients with bloodstream infections due to carbapenemase-producing *Enterobacteriaceae* (INCREMENT): a retrospective cohort study. Lancet Infect Dis 2017 Jul;17(7):726-734.

[17] Paul M, Carmeli Y, Durante-Mangoni E, Mouton JW, Tacconelli E, Theuretzbacher U, et al. Combination therapy for carbapenem-resistant Gram-negative bacteria. J Antimicrob Chemother 2014;69:2305-9.

[18] Zusman O, Altunin S, Koppel F, Benattar YD, Gedik H, Paul M. Polymyxin monotherapy or in combination against carbapenem-resistant bacteria: systematic review and meta-analysis. J Antimicrob Chemother 2017;72:29-39.

[19] SurveyMonkey. Free online survey & questionnaire tool [Internet]. San Mateo, California, USA: SurveyMonkey Inc.; 1999-2017 [cited 2017 Aug 12]. Available from: http://www.surveymonkey.com

[20] Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect 2012;18:268-81.

[21] Durante-Mangoni E, Signoriello G, Andini R, Mattei A, De Cristofordo M, Murino P, et al. Colistin and rifampicin compared with colistin alone for the treatment of serious infections due to extensively drug-resistant *Acinetobacter baumannii*: a multicenter, randomized clinical trial. Clin Infect Dis 2013;57:349-58.

[22] Aydemir H, Akduman D, Piskin N, Comert F, Horuz E, Terzi A, et al. Colistin vs. the combination of colistin and rifampicin for the treatment of carbapenem-resistant *Acinetobacter baumannii* ventilator-associated pneumonia. Epidemiol Infect 2013;141:1214-22.

[23] Sirijatuphat R, Thamlikitkul V. Preliminary study of colistin versus colistin plus fosfomycin for treatment of carbapenem-resistant *Acinetobacter baumannii* infections. Antimicrob Agents Chemother 2014;58:5598-601.

[24] Petrosillo N, Ioannidou E, Falagas ME. Colistin monotherapy vs. combination therapy: evidence from microbiological, animal and clinical studies. Clin Microbiol Infect 2008;14:816-27.

[25] Paul M, Lador A, Grozinsky-Glasberg S, Leibovici L. Beta lactam antibiotic monotherapy versus beta lactam-aminogycoside antibiotic combination therapy for sepsis. Cochrane Database Sys Rev [Internet]. 2014 [cited 2017 Sep 3]. Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003344.pub3/full

[26] Paul M, Dickstein Y, Schlesinger A, Grozinsky-Glasberg S, Soares-Weiser K, Leibovici L. Beta-lactam versus beta-lactam-aminoglycoside combination therapy in cancer patients with neutropenia. Cochrane Database Sys Rev [Internet]. 2013 [cited 2017 Sep 3]. Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003038.pub2/full

[27] Marcus R, Paul M, Elphick H, Leibovici L. Clinical implications of beta-lactam-aminoglycoside synergism: systematic review of randomised trials. Int J Antimicrob Agents 2011;37:491-503.

[28] Bliziotis IA, Samonis G, Vardakas GZ, Chrysanthopoulou S, Falagas ME. Effect of aminoglycoside and beta-lactam combination therapy versus beta-lactam monotherapy on the emergence of antimicrobial resistance: a meta-analysis of randomized, controlled trials. Clin Infect Dis 2005;41:149-58.

[29] Vardakas KZ, Trigkidis KK, Boukouvala E, Falagas ME. *Clostridium difficile* infection following systemic antibiotic administration in randomised controlled trials: a systematic review and meta-analysis. Int J Antimicrob Agents 2016;48:1-10.

[30] Schwaber MJ, Klarfeld-Lidji S, Navon-Venezia S, Schwartz D, Leavitt A, Carmeli Y. Predictors of carbapenem-resistant *Klebsiella pneumoniae* acquisition among hospitalized adults and effect of acquisition on mortality. Antimicrob Agents Chemother 2008;52:1028-33.

429 **Table 1.** Importance of different factors when choosing an antibiotic for treating infections caused by carbapenem-resistant Gram-negative bacilli

Factor	n (%), N=110		
	Not important	**Moderately important**	**Very important**
Source of infection (e.g. pneumonia, urinary tract infection etc.)	1 (0.9)	15 (13.6)	94 (85.5)
Severity of the disease	2 (1.8)	15 (13.6)	93 (84.5)
Immune status of the patient	0 (0)	50 (45.5)	60 (54.5)
Renal or hepatic impairment	2 (1.8)	53 (48.2)	55 (50)
Type of isolated microorganism (e.g. *K. pneumoniae*, *P. aeruginosa*, etc.)	1 (0.9)	25 (22.7)	84 (76.4)
Type of carbapenemase (e.g. KPC, NDM etc.)	14 (12.7)	38 (34.5)	58 (52.7)
Minimum inhibitory concentration (MIC) for the antibiotic	2 (1.8)	17 (15.5)	91 (82.7)
Pharmacokinetic/pharmacodynamic (PK/PD) profile of the antibiotic	1 (0.9)	24 (21.8)	85 (77.3)
Toxicity profile of the antibiotic	4 (3.6)	53 (48.2)	53 (48.2)
Interactions of the antibiotic with other drugs	15 (13.6)	56 (50.9)	39 (35.5)

KPC: *Klebsiella pneumoniae* carbapenemase, NDM: New Delhi metallo-beta-lactamase

430 **Table 2**. Polymyxin use in participating centers

Characteristic	Number of hospitals
Main polymyxin used	N=112
Colistin	105 (93.8%)
Polymyxin B	1 (0.9%)
Both polymyxins	6 (5.4%)
Use of a loading dose	99/111 (89.2%) [1]
Colistin schedule [2]	N=110
Twice daily	75 (68.2%)
Thrice daily	35 (31.8%)
Therapeutic drug monitoring (TDM)	N=112
Routinely	5 (4.5%)
In specific situations	13 (11.6%)
Do not use	41 (36.6%)
No access to TDM for polymyxins	53 (47.3%)
Aerosolised polymyxin with systemic antibiotics for ventilator-associated pneumonia (VAP)	86/112 (76.8%)

431

432 [1] 9 million international units in 96 hospitals

433 [2] Polymyxin B was given as a 2.5 or 3 mg/kg dose twice daily (N=6).

434 **Table 3.** Carbapenem-containing combination regimens for carbapenem-resistant Gram-negative

435 bacilli

Carbapenem used for combination therapy	**n (%), N=109**
Doripenem	2 (1.8)
Imipenem	26 (23.9)
Meropenem	100 (91.7)
Ertapenem	7 (6.4)
Double-carbapenem combination therapy (ertapenem combined with another carbapenem)	26 (23.9)
No carbapenem-containing combinations	8 (7.3)
Carbapenem MIC at which its use is considered	**n (%), N=106**
MIC ≤ 4 mg/l	10 (9.4)
MIC ≤ 8 mg/l	47 (44.3)
MIC ≤ 16 mg/l	20 (18.9)
MIC ≤ 32 mg/l	10 (9.4)
Carbapenem use regardless of the MIC value	19 (17.9)
Use of prolonged carbapenem infusion in combinations	**n (%), N=105**
Yes	76 (72.4)
No	29 (27.6)

436

437 MIC: minimum inhibitory concentration

438 **Table 4.** Indications for use of combination therapy

Source of infection	**n (%), N=110**
Complicated urinary tract infections	41 (37.3)
Pneumonia	92 (83.6)
Intraabdominal infections	80 (72.7)
Skin and soft tissue infections	42 (38.2)
Central nervous system infections	96 (87.3)
Bacteremia of any source	91 (82.7)
Bacteria	**n (%), N=109**
Carbapenem-resistant *Enterobacteriaceae*	98 (89.9)
Carbapemem-resistant XDR *P. aeruginosa*	93 (85.3)
Carbapenem-resistant XDR *A. baumannii*	90 (82.5)

XDR: extensively drug-resistant

439

440 **Table 5.** Most frequent antibiotic regimens for targeted treatment for infections caused by

441 carbapenem-resistant *Enterobacteriaceae* [1]

Total N=114	**cUTI**	**Pneumonia**	**IAI**	**SSTI**	**CNSI**	**Bacteremia**
Monotherapy (N=57, 50%)						
POL	20 (35.1)	18 (31.6)	10 (17.5)	12 (21.2)	7 (12.3)	17 (29.8)
TIG	5 (8.8)	9 (15.8)	20 (35.1)	20 (35.1)	3 (5.3)	8 (14)
AMG	40 (70.2)	6 (10.5)	8 (14)	7 (12.3)	3 (5.3)	14 (24.6)
FOS	19 (33.3)	1 (1.8)	1 (1.8)	0 (0)	3 (5.3)	3 (5.3)
CAZ/AVI	20 (35.1)	16 (28.1)	17 (29.8)	16 (28.1)	5 (8.8)	17 (29.8)
Double combination therapy (N=105, 92.1%)						
POL + TIG	13 (10)	43 (41)	61 (58.1)	40 (38.1)	9 (8.6)	34 (32.4)
POL + CARB	53 (50.5)	63 (60)	52 (49.5)	35 (33.3)	52 (49.5)	67 (63.9)
TIG + CARB	6 (5.7)	24 (22.9)	40 (38.1)	26 (24.8)	9 (8.6)	21 (20)
TIG + AMG	9 (8.6)	12 (11.4)	32 (30.5)	26 (24.8)	3 (2.9)	18 (17.1)
AMG + FOS	34 (32.4)	8 (7.6)	8 (7.6)	8 (7.6)	7 (6.7)	18 (17.1)
Triple combination therapy (N=72, 63.2%)						
POL + TIG + CARB	12 (16.7)	39 (54.2)	36 (50)	22 (30.6)	21 (29.2)	40 (55.6)
POL + TIG + AMG	9 (12.5)	17 (23.6)	17 (23.6)	6 (8.3)	6 (8.3)	21 (29.2)
POL + TIG + FOS	4 (5.6)	14 (19.4)	8 (11.1)	6 (8.3)	8 (11.1)	13 (18.1)
POL + AMG + FOS	17 (23.6)	7 (9.7)	4 (5.6)	2 (2.8)	4 (5.6)	15 (20.8)
DOUBLE CARB + POL	8 (11.1)	11 (15.3)	7 (9.7)	5 (6.9)	12 (16.7)	13 (18.1)

cUTI: complicated urinary tract infection, IAI: intraabdominal infection, SSTI: skin and soft tissue infection, CNSI: central nervous system infection, POL: polymyxin, TIG: tigecycline, AMG: aminoglycoside, FOS: fosfomycin, CAZ/AVI: ceftazidime/avibactam, CARB: carbapenem

[1] Respondents could choose more than one treatment regimen. Detailed data on all antibiotic

regimens are presented in Supplementary File, Table S4.

442

443 **Table 6.** Most frequent antibiotic regimens of targeted treatment of infections caused by extensively

444 drug-resistant carbapenem-resistant *P. aeruginosa* [1]

Total N=110	**cUTI**	**Pneumonia**	**IAI**	**SSTI**	**CNSI**	**Bacteremia**
Monotherapy (N=66, 60%)						
POL	23 (34.8)	15 (22.7)	12 (18.2)	14 (21.2)	7 (10.6)	13 (19.7)
AMG	32 (48.5)	4 (6.1)	6 (9.1)	5 (7.6)	1 (1.5)	8 (12.1)
FOS	11 (16.7)	0 (0)	0 (0)	1 (1.5)	1 (1.5)	1 (1.5)
TOL/TAZ	41 (62.1)	27 (40.9)	28 (42.4)	23 (34.8)	10 (15.2)	20 (30.3)
Double combination therapy (N=95, 86.4%)						
POL + CARB	41 (43.2)	58 (61.1)	51 (53.7)	40 (42.1)	43 (45.2)	52 (54.7)
POL + RIF	6 (6.3)	15 (15.8)	9 (9.5)	10 (10.5)	12 (12.6)	13 (13.7)
POL + AMG	33 (34.7)	27 (28.4)	32 (33.7)	23 (24.2)	9 (9.5)	35 (36.8)
POL + FOS	30 (31.6)	26 (27.4)	18 (18.9)	19 (20)	15 (15.8)	22 (23.2)
AMG + FOS	30 (31.6)	12 (12.6)	11 (11.6)	12 (12.6)	7 (7.4)	16 (16.8)
Triple combination therapy (N=48, 43.6%)						
POL + CARB + RIF	7 (14.6)	17 (35.4)	14 (29.2)	13 (27.1)	16 (33.3)	15 (31.3)
POL + CARB + AMG	15 (31.3)	16 (33.3)	16 (33.3)	13 (27.1)	9 (18.8)	20 (41.7)
POL + CARB + FOS	17 (35.4)	12 (25)	10 (20.8)	9 (18.8)	14 (29.2)	12 (25)
POL + AMG + RIF	5 (10.4)	4 (8.3)	7 (14.6)	5 (10.4)	8 (16.7)	11 (22.9)
POL + AMG + FOS	12 (25)	9 (18.8)	6 (12.5)	5 (10.4)	7 (14.6)	10 (20.8)

cUTI: complicated urinary tract infection, IAI: intraabdominal infection, SSTI: skin and soft tissue infection, CNSI: central nervous system infection, POL: polymyxin, AMG: aminoglycoside, FOS: fosfomycin, TOL/TAZ: ceftolozane/tazobactam, CARB: carbapenem, RIF: rifampicin

[1] Respondents could choose more than one treatment regimen. Detailed data on all antibiotic regimens are presented in Supplementary File, Table S5.

445 **Table 7.** Most frequent antibiotic regimens for targeted treatment of infections caused by

446 extensively drug-resistant carbapenem-resistant *A. baumannii*[1]

Total N=96	**cUTI**	**Pneumonia**	**IAI**	**SSTI**	**CNSI**	**Bacteremia**
Monotherapy (N=46, 47.9%)						
POL	30 (65.2)	21 (45.7)	16 (34.8)	18 (39.1)	13 (28.3)	19 (41.3)
TIG	4 (8.7)	5 (10.9)	14 (30.4)	16 (34.8)	1 (2.2)	3 (6.5)
AMG	29 (63)	5 (10.9)	5 (10.9)	5 (10.9)	1 (2.2)	9 (19.6)
Double combination therapy (N=80, 83.3%)						
POL + TIG	18 (22.5)	37 (46.3)	39 (48.8)	33 (41.3)	8 (10)	26 (32.5)
POL + CARB	35 (43.8)	42 (52.5)	40 (50)	33 (41.3)	35 (43.8)	48 (60)
POL + RIF	15 (18.8)	24 (30)	15 (18.8)	15 (18.8)	17 (21.3)	19 (23.8)
POL + FOS	20 (25)	16 (20)	9 (11.3)	11 (13.8)	10 (12.5)	14 (17.5)
TIG + CARB	4 (5)	14 (17.5)	19 (23.8)	14 (17.5)	7 (8.8)	13 (16.3)
Triple combination therapy (N=43, 44.8%)						
POL + TIG + CARB	13 (30.2)	24 (55.8)	24 (55.8)	18 (41.9)	15 (34.9)	22 (51.2)
POL + TIG + RIF	7 (16.3)	18 (41.9)	13 (30.2)	15 (34.9)	11 (25.6)	14 (32.6)
POL + TIG + AMG	5 (11.6)	8 (18.6)	10 (23.2)	7 (16.3)	5 (11.6)	15 (34.9)
POL + TIG + FOS	6 (14)	7 (16.3)	9 (20.9)	6 (14)	7 (16.3)	7 (16.3)
TIG + RIF + AMG	5 (11.6)	5 (11.6)	7 (16.3)	7 (16.3)	2 (4.7)	9 (20.9)

cUTI: complicated urinary tract infection, IAI: intraabdominal infection, SSTI: skin and soft tissue infection, CNSI: central nervous system infection, POL: polymyxin, TIG: tigecycline, AMG: aminoglycoside, CARB: carbapenem, RIF: rifampicin, FOS: fosfomycin

[1] Respondents could choose more than one treatment regimen. Detailed data on all antibiotic regimens are presented in Supplementary File, Table S6.

447