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## 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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## 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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**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;24:1070**

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## 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](#)).

### 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 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 important, whereas 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 loading dose of 9 million international units (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 aerosolized 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 CRGNB, most respondents considered using a carbapenem-containing combination when the carbapenem MIC was  $\leq 8$  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 bacteraemia, pneumonia and central nervous system infections and for *Enterobacteriaceae*, *P. aeruginosa* and *A. baumannii* similarly (Table 4). When asked on what the decision to use combination rather than monotherapy was based, 63/110 (57.3%) declared they relied on *in vitro* studies, 69.1% relied on observational studies, 55.5% relied on RCTs, 68.2% on systematic reviews and 53.6% on personal experience. The intended goal of combination therapy was most commonly to improve the 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%).

**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. <i>Klebsiella pneumoniae</i> , <i>Pseudomonas aeruginosa</i> , etc.)	1 (0.9)	25 (22.7)	84 (76.4)
Type of carbapenemase (e.g. <i>Klebsiella pneumoniae</i> carbapenemase, New Delhi metallo- $\beta$ -lactamase 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 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)

### 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%) (see Supplementary material, 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 intra-abdominal 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 bacteraemia 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 aminoglycoside 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 bacteraemia in 55.6% (40/72) of hospitals) or an aminoglycoside (e.g. for treating bacteraemia 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 bacteraemia in 54.7% (52/95) of hospitals), with 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 cUTIs. Aminoglycosides (29/46, 63%) and polymyxins (30/46, 65.2%) were the main treatment for cUTIs and

**Table 2**  
Polymyxin use in participating centres

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%) <sup>a</sup>
Colistin schedule <sup>b</sup>	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%)
Aerosolized polymyxin with systemic antibiotics for ventilator-associated pneumonia	86/112 (76.8%)

<sup>a</sup> 9 million international units in 96 hospitals.<sup>b</sup> Polymyxin B was given as a 2.5 or 3 mg/kg dose twice daily (n = 6).**Table 3**  
Carbapenem-containing combination regimens for carbapenem-resistant Gram-negative 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)

**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)
Intra-abdominal infections	80 (72.7)
Skin and soft-tissue infections	42 (38.2)
Central nervous system infections	96 (87.3)
Bacteraemia of any source	91 (82.7)
Bacteria	n (%), N = 109
Carbapenem-resistant <i>Enterobacteriaceae</i>	98 (89.9)
Carbapenem-resistant extensively drug-resistant <i>Pseudomonas aeruginosa</i>	93 (85.3)
Carbapenem-resistant extensively drug-resistant <i>Acinetobacter baumannii</i>	90 (82.5)

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 bacteraemia 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 cUTIs was also very common in Kosovo, Slovenia, Spain and the USA. There were no major differences in the selection of most commonly used antibiotics, but some distinctions between countries were noted. Ceftolozane/tazobactam was commonly used for treatment of cUTIs and pneumonia caused by XDR CRPa in France, Italy, Spain and the USA, whereas 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 the [Supplementary material \(Tables S7–S14\)](#).

#### 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 bacteraemia, pneumonia and central nervous system infections. 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 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, whereas ceftolozane/tazobactam was used for monotherapy of infections caused by XDR CRPa in all countries except Israel. Among polymyxins, colistin was almost universally used, mostly dosed twice daily after the initial 9 million international units 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 scientific evidence (i.e. RCTs). In fact, there were three RCTs published at the time of the survey that tested only two interventions, only for *A. baumannii*—colistin/rifampicin versus colistin [21,22] and colistin/fosfomycin versus colistin [23]. There were no published RCTs on carbapenem combination therapy for CRGNBs (two underway at 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 an individual with sepsis. Even if combination therapy were to be timed perfectly, drug penetration to the site of infection cannot be controlled. Despite many *in vitro* studies demonstrating synergistic interactions and prevention of resistant strain



**Table 5**  
Most frequent antibiotic regimens for targeted treatment for infections caused by carbapenem-resistant *Enterobacteriaceae*<sup>a</sup>

Total N = 114	cUTI	Pneumonia	IAI	SSTI	CNSI	Bacteraemia
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)

Abbreviations: cUTI, complicated urinary tract infection; IAI, intra-abdominal 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.

<sup>a</sup> Respondents could choose more than one treatment regimen. Detailed data on all antibiotic regimens are presented in the [Supplementary material \(Table S4\)](#).

**Table 6**  
Most frequent antibiotic regimens for targeted treatment of infections caused by extensively drug-resistant carbapenem-resistant *Pseudomonas aeruginosa*<sup>a</sup>

Total N = 110	cUTI	Pneumonia	IAI	SSTI	CNSI	Bacteraemia
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)

Abbreviations: cUTI, complicated urinary tract infection; IAI, intra-abdominal 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.

<sup>a</sup> Respondents could choose more than one treatment regimen. Detailed data on all antibiotic regimens are presented in the [Supplementary material \(Table S5\)](#).

**Table 7**  
Most frequent antibiotic regimens for targeted treatment of infections caused by extensively drug-resistant carbapenem-resistant *Acinetobacter baumannii*<sup>a</sup>

Total N = 96	cUTI	Pneumonia	IAI	SSTI	CNSI	Bacteraemia
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)

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

<sup>a</sup> Respondents could choose more than one treatment regimen. Detailed data on all antibiotic regimens are presented in the [Supplementary material \(Table S6\)](#).

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 therapy [21–23].

Carbapenems, mainly meropenem, were the most common antibiotics added to polymyxins in combination therapy regimens. Carbapenems are among the 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 colonization 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 treatment strategies. However, we made it clear in the online survey and in correspondence with respondents that the survey intended to reflect actual common practice at the participating hospital.

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

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## Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.cmi.2018.01.015>.

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