Clinical Microbiology and Infection xxx (xxxx) xxx

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Original Article

Clinical management of severe infections caused by carbapenem-resistant gram-negative bacteria: a worldwide cross-sectional survey addressing the use of antibiotic combinations

Elena Carrara [1, *, †], Alessia Savoldi [1, †], Laura J.V. Piddock [2], Francois Franceschi [2], Sally Ellis [2], Mike Sharland [3], Adrian John Brink [4], Patrick N.A. Harris [5, 6], Gabriel Levy-Hara [7], Anusha Rohit [8], Constantinos Tsioutis [9], Hiba Zayyad [10], Christian Giske [11], Margherita Chiamenti [1], Damiano Bragantini [1], Elda Righi [1], Anna Gorska [1], Evelina Tacconelli [1, 12, 13]

[1] *Division of Infectious Diseases, Department of Diagnostic and Public Health, University of Verona, Verona, Italy*
[2] *Global Antibiotic Research & Development Partnership (GARDP), Geneva, Switzerland*
[3] *Institute of Infection and Immunity, St George's University London, London, UK*
[4] *Division of Medical Microbiology, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa*
[5] *University of Queensland, Faculty of Medicine, UQ Centre for Clinical Research, QLD, Australia*
[6] *Central Microbiology, Pathology Queensland, Royal Brisbane & Women's Hospital, QLD, Australia*
[7] *Infectious Diseases Unit, Hospital Carlos G Durand, Buenos Aires, Argentina*
[8] *Department of Microbiology and Infection Control, The Madras Medical Mission, Adjunct Professor, NITTE University, Chennai, India*
[9] *School of Medicine, European University Cyprus, Nicosia, Cyprus*
[10] *Infectious Diseases Unit, The Baruch Padeh Medical Center, Poriya Hospital, M.P. the Lower Galilee, Tiberias, Israel*
[11] *Division of Clinical Microbiology, Department of Laboratory Medicine, Karolinska Institutet, Stockholm, Sweden*
[12] *Division of Infectious Diseases, Department of Internal Medicine I, German Centre for Infection Research, University of Tübingen, Tübingen, Germany*
[13] *German Centre for Infection Research (DZIF), Clinical Research Unit for Healthcare Associated Infections, Tübingen, Germany*

ARTICLE INFO

Article history:
Received 18 March 2021
Received in revised form
23 April 2021
Accepted 1 May 2021
Available online xxx

Editor: L. Leibovici

Keywords:
Antibiotic resistance
Bacterial infections
Carbapenem-resistant gram-negative
Combination therapy
Cross-sectional survey

ABSTRACT

Objectives: Optimal treatment of carbapenem-resistant Gram-negative bacteria (CR-GNB) infections is uncertain because of the lack of good-quality evidence and the limited effectiveness of available antibiotics. The aim of this survey was to investigate clinicians' prescribing strategies for treating CR-GNB infections worldwide.

Methods: A 36-item questionnaire was developed addressing the following aspects of antibiotic prescribing: respondent's background, diagnostic and therapeutic availability, preferred antibiotic strategies and rationale for selecting combination therapy. Prescribers were recruited following the snowball sampling approach, and a post-stratification correction with inverse proportional weights was used to adjust the sample's representativeness.

Results: A total of 1012 respondents from 95 countries participated in the survey. Overall, 298 (30%) of the respondents had local guidelines for treating CR-GNB at their facility and 702 (71%) had access to Infectious Diseases consultation, with significant discrepancies according to country economic status: 85% (390/502) in high-income countries versus 59% (194/283) in upper-medium-income countries and 30% (118/196) in lower-middle-income countries/lower-income-countries). Targeted regimens varied widely, ranging from 40 regimens for CR-*Acinetobacter* spp. to more than 100 regimens for CR-*Enterobacteriaceae*. Although the majority of respondents acknowledged the lack of evidence behind this choice, dual combination was the preferred treatment scheme and carbapenem-polymyxin was the most prescribed regimen, irrespective of pathogen and infection source. Respondents noticeably disagreed around the meaning of 'combination therapy' with 20% (150/783) indicating the simple addition of multiple compounds, 42% (321/783) requiring the presence of *in vitro* activity and 38% (290/783) requiring *in vitro* synergism.

* Corresponding author: Elena Carrara, Division of Infectious Diseases, Department of Diagnostic and Public Health, University of Verona, P.Le L.A. Scuro 10, 37134, Verona, Italy.
E-mail address: elena.carrara@univr.it (E. Carrara).
† Elena Carrara and Alessia Savoldi contributed equally.

https://doi.org/10.1016/j.cmi.2021.05.002

Please cite this article as: Carrara E et al., Clinical management of severe infections caused by carbapenem-resistant gram-negative bacteria: a worldwide cross-sectional survey addressing the use of antibiotic combinations, Clinical Microbiology and Infection, https://doi.org/10.1016/j.cmi.2021.05.002

Conclusions: Management of CR-GNB infections is far from being standardized. Strategic public health focused randomized controlled trials are urgently required to inform evidence-based treatment guidelines. **Elena Carrara, Clin Microbiol Infect 2021;▪:1**

Introduction

In 2017, WHO prioritized carbapenem-resistant Gram-negative bacteria (CR-GNB) *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacteriaceae* as species of critical importance for research and development of new and effective antibiotics [1]. Only a few new antibiotics with the potential to treat those bacteria have come to the market, and fewer still are in the later stages of their clinical development [2]. However, none of these new compounds have been tested in large randomized clinical trials enrolling patients with CR-GNB infections before their approval. Robust evidence of their effectiveness and superiority to conventional and available antibiotics still needs to be established [2]. Existing studies on the treatment of CR-GNB infections are mostly observational and limited by small sample sizes and the lack of adjustment for major confounders [3–5]. The few available guidance documents, although recognizing the low quality of the evidence, suggest that combination therapy might be superior to monotherapy for severe infections [6,7]. However, because of the very limited evidence, it is difficult to provide precise recommendations as to the specific antibiotic combinations that should be adopted for treating the possible clinical scenarios. In an era where the rational use of the few available antibiotics is of utmost importance, clinicians treating severe infections caused by CR-GNB have to make decisions on which antibiotics to use on a daily basis without the support of evidence-based recommendations and heterogeneous access to diagnostic and therapeutic resources [8].

The main goal of this study was to conduct a cross-sectional survey to assess antibiotic prescribing patterns among clinicians worldwide with a particular focus on the use of combination therapy.

Materials and methods

Target population and sampling

The target population of the survey was clinicians managing patients with severe infections caused by CR-GNB in their current practice (a minimum of five cases of any CR-GNB infection per year was set as a limit to participate in the survey). Participants were sampled from the target population in accordance with the 'snowball sampling' approach, which relies essentially on two key phases: (a) the recruitment of a core sample of individuals having similar characteristics to the population target (a core-expert group of 99 prescribers selected from surveillance networks and scientific societies) and (b) the referral process, in which this group nominates, through various transmission routes, other individuals who meet the eligibility criteria [9–11]. The objective was to involve at least one representative from all the countries where diagnostic capabilities for detecting carbapenem-resistance are in place (the full process is detailed in the Supplementary material, Tables S1a–S2).

Survey development, validation and distribution

The survey content was developed and validated in accordance with current guidelines on surveys in medical research [12–16]. The final questionnaire consisted of 36 open-ended, single- and multiple-choice items addressing four major aspects of antibiotic prescribing: respondent's background, diagnostic and therapeutic availability, preferred antibiotic strategies and rationale for selecting combination therapy. The questionnaire was validated by experts from different geographic areas and disseminated via a *Survey Monkey* link (https://it.surveymonkey.com) during a 10-week period (the final questionnaire and details of the development and validation process are detailed in the Supplementary material, Fig. S1 and Table S1b).

Statistical analysis

Anonymous data were automatically entered by the survey software into an electronic database. Both complete and incomplete questionnaires were included for analysis. Results were expressed as frequency of responses for each question or as median with interquartile range, when appropriate. The number of total responses for each question item was used as denominator. Responses were computed overall or stratified by four subgroups of interest: WHO region; income category (in accordance with the 2019 World Bank Classification); patients' age (neonates: 0–1 month, children: >1 month to 14 years, adults: >14 years); respondents' antibiotic prescribing frequency (low rate prescribers: from 1 to 4 cases per year; medium rate prescribers: from 5 to 20 cases per year, high rate prescribers: more than 20 cases per year). Between groups comparisons were computed using χ^2 and a two-sided p value $< 0{\cdot}05$ was regarded as significant. Data were analysed using STATA 15 (Statacorp LP, College Station, TX, USA). Figures were created using Python 3.7.3 and Matplotlib package v. 3.2.1.

To address the imbalance due to the non-probabilistic sampling method, a post-stratification correction was applied for preselected question items according to the respondent's country and hospital. In the post-stratification analysis, the weights were adjusted so that the totals in each group are equal to the known population totals [17,18].

Ethics approval

Official submission to the Ethics Committee was deemed unnecessary because the participation into the survey was voluntary and anonymous.

Results

Respondents' characteristics

The survey was disseminated during a 10-week period, from 15 April until 28 June 2019. In total, 1012 respondents from 95 countries and 687 hospitals returned the questionnaire with an average completion rate of 86%. The distribution of respondents according to the four main categories is shown in Table 1. The majority of respondents were specialized in Infectious Diseases (548; 54%), were employed in tertiary-level hospitals (810; 81%) and in teaching or university-affiliated hospitals (859; 85%). The

Please cite this article as: Carrara E et al., Clinical management of severe infections caused by carbapenem-resistant gram-negative bacteria: a worldwide cross-sectional survey addressing the use of antibiotic combinations, Clinical Microbiology and Infection, https://doi.org/10.1016/j.cmi.2021.05.002

Table 1
Number of respondents stratified by the four subgroups of interest

	Respondents, *n* (%)
WHO region	
Africa	64 (6·0)
Americas	205 (20·5)
Eastern Mediterranean	116 (11·5)
Europe	444 (44·0)
South East Asia	95 (9·3)
Western Pacific	88 (8·7)
Total	1012 (100)
Patients' age	
Adults	867 (85·6)
Paediatric population	145 (14·3)
Children	110 (10·9)
Neonates	35 (3·5)
Total	1012 (100)
Income category	
High-income countries	512 (50·6)
Upper-middle income countries	296 (29·2)
Lower-middle-income/Low-income countries	204 (20·1)
Total	1012 (100)
Prescribing frequency[a]	
Low-rate prescribers	257 (25·4)
Medium-rate prescribers	416 (41·1)
High-rate prescribers	283 (28·0)
Not specified	56 (5·5)
Total	**1012 (100)**

[a] Low-rate prescribers: from 1 to 4 cases per year; medium-rate prescribers: from 5 to 20 cases per year, high-rate prescribers: more than 20 cases per year.

distribution of respondents by country and specialty is displayed in the Supplementary material (Table S3 and Fig. S2).

Local prevalence of carbapenem resistance in GNB was reported with high variability among countries and among hospitals within the same country and, in some cases, even within the same region (see Supplementary material, Table S4). Overall, 20% (193/974) of respondents did not have data on local phenotypic drug resistance rates; the genotypic mechanism of resistance was not known by 32% (299/974) of respondents. Relative to CR-*Klebsiella pneumoniae*, the production of serine-carbapenemases was the most frequent resistance mechanism in the American Region (93/203; 46%), while the production of metallo-β-lactamases was the most common resistance mechanism in South East Asia (39/90; 43%) and Western Pacific (34/77; 44%) Regions (see Supplementary material, Table S5).

Availability of diagnostics, therapeutics and treatment guidelines

Availability of antibiotics was heterogeneous across countries and, often, also within the same country. Gentamicin, trimethoprim-sulfamethoxazole, rifampin, amikacin and carbapenems were available in more than 95% of the surveyed countries, regardless of income. Carbapenems were placed under restrictive policies in 78% (32/41) of high-income countries; in 89% (25/28) of upper-middle-income countries and in 61% (16/26) of lower-middle-income countries/lower-income countries. Colistin was available in 83% (79/94) of the surveyed countries, with restrictive policies in place in 90% (37/41) of high-income countries, 91% (25/28) of upper-middle-income countries and 77% (20/26) of lower-middle-income countries/lower-income countries. Among the drugs that most recently entered the market, ceftazidime/avibactam was available in 33% (32/94) of countries (26/41, 63% high-income countries; 4/28, 14% upper-middle-income countries and 2/26, 8% lower-middle-income countries/lower-income countries). Fewer than ten respondents had access to the most recently approved antibiotic compounds (meropenem/vaborbactam, eravacycline and plazomicin). Availability of antibiotics by country and income is detailed in the Supplementary material (Fig. S3a–c).

Only 30% (298/981) of respondents reported that local guidelines for treating CR-GNB were available, with no significant difference according to income category (see Supplementary material, Table S6). Active Infectious Diseases consultation services were significantly more common among respondents from high-income countries (390/582; 85%) compared with respondents from upper-middle-income countries (194/283; 59%) and lower-middle-income countries/lower-income countries (118/196; 30%) ($p < 0·01$).

As for diagnostic resources, 77% (767/908) of respondents had access to standard susceptibility testing at a local level with no differences according to income status. More complex diagnostics (matrix-assisted laser desorption/ionization time-of flight and nucleic acid amplification testing) were significantly more accessible in high-income countries compared with upper-middle-income countries and lower-middle-income countries/lower-income countries (Table 2). As a direct consequence of this variability, the timing of diagnosis was considerably longer in low-resource settings, with 23% (110/473) of respondents from those countries receiving blood cultures more than 72 hours after sampling, compared with only 7% (37/500) in high-income countries (Table 3).

Prescribing strategies

Colistin and tigecycline were preferably prescribed in combination by 73% (492/671) and 71% (330/647) of respondents, followed by combination fosfomycin (53%; 244/463), ceftazidime/avibactam (45%; 145/333), polymyxin B (35%; 104/297) and gentamicin (34%; 264/770) (Table 4).

As for prescribing strategies, carbapenem loading dose and extended infusion were adopted more frequently by high-rate prescribers compared with clinicians who dealt with CR-GNB infections less frequently. Similarly, higher-dose tigecycline and loading dose of polymyxins and tigecycline, were significantly more frequent in the high-rate-prescribers group compared with the others ($p < 0·01$ for all comparisons; see Supplementary material, Table S7).

The decision to start empirical coverage for CR-GNB was significantly more common in prescribers from high-income countries and directly associated with patients' clinical severity. Local epidemiological data and/or individual risk factors played less of a role in driving the decision to start empiric coverage (Fig. 1).

As for targeted therapy, the preferred strategy was the combination of two antibiotics (between 35% and 45% of respondents depending on sepsis sources or bacterial species). The use of single-antibiotic therapy was second in preference, especially for CR-*Acinetobacter* spp. and CR-*Pseudomonas* spp. (23%–37% and 26%–35% of respondents, respectively, depending on the sepsis source). A combination of three antibiotics was regarded as the preferred strategy by a lower number of respondents (15%–20% depending on sepsis sources or pathogen type). Full results on preferred therapeutic choices are displayed in the Supplementary material (Tables S8–S10).

When considering the components in the targeted combination regimens, respondents selected an extremely wide spectrum of distinct combinations. The number of regimens ranged from 40 regimens in CR-*Acinetobacter* spp. to more than 100 regimens in CR-*Enterobacteriaceae*. Overall, the combination 'carbapenem plus a polymyxin' was the most prescribed option for treating sepsis, irrespective of bacterial species or sepsis source (full results on targeted treatment are presented in the Supplementary material, Fig. S4a–c and Tables S11–S13).

Only 80 responses were available regarding treatment options in children and neonates; similar to the adult population, the most

Please cite this article as: Carrara E et al., Clinical management of severe infections caused by carbapenem-resistant gram-negative bacteria: a worldwide cross-sectional survey addressing the use of antibiotic combinations, Clinical Microbiology and Infection, https://doi.org/10.1016/j.cmi.2021.05.002

Table 2
Availability of diagnostic tools for detecting CR-GNB in blood cultures

Diagnostic tool	HIC (n = 469; 45·8%)	UMIC (n = 268; 26·3%)	LMIC/LIC (n = 171; 27·9%)	Overall (n = 908)	p value
Standard AST	373 (75·2%)	238 (82·6%)	156 (76·3%)	767 (77·5%)	NS
MALDI-TOF	277 (58·8%)	61 (17·7%)	15 (2·8%)	353 (32·4%)	<0·001
Rapid phenotypic test from blood isolates	142 (32·3%)	61 (21·1%)	15 (1·5%)	218 (20·8%)	<0·001
NAAT	217 (47·2%)	45 (15·4%)	21 (9·6%)	283 (28·4%)	<0·001
In all CR-GNB strains	157 (26·6%)	16 (6·4%)	11 (5·8%)	184 (15·5%)	<0·001
only in selected cases	60 (20·6%)	29 (9·1%)	10 (3·7%)	12·9 (99)	0·008
Internal testing facilities not available	34 (5·3%)	38 (14·0%)	25 (21·7%)	10· 6 (97)	<0·001

Abbreviations: AST, antimicrobial susceptibility test; CR-GNB, carbapenem-resistant Gram-negative bacteria; HIC, high-income countries; LMI/LC, lower-middle-income/low-income countries; MALDI-TOF, matrix-assisted laser desorption/ionization time-of flight; NAAT, nucleic acid amplification testing; NS, non-significant; UMIC, upper-middle-income countries.
Frequencies of positive responses are presented as percentages of the total of responses from each income category after adopting post-stratification correction by hospital and country.

Table 3
Time needed by laboratories to inform on the positivity of blood cultures

Time to positive blood cultures	Income category; n (%) of country			p value
	HIC (n = 500; 51·5%)	UMIC (n = 282; 27·2%)	LMI/LIC (n = 191; 25·3%)	
Within 36 hours	172 (41·2%)	70 (21·6%)	51 (20·8%)	0·01
Within 48 hours[a]	349 (73·2%)	139 (40·0%)	93 (42·5%)	<0·001
Within 72 hours[a]	463 (80·1%)	224 (52·0%)	139 (59·8%)	<0·001
Within 96 hours[a]	494 (99·1%)	260 (91·8%)	174 (80·4%)	<0·001
More than 96 hours	6 (0·9%)	22 (8·2%)	17 (19·6%)	<0·001

Abbreviations: HIC, high-income countries; LMI/LC, lower-middle-income/low-income countries; UMIC, upper-middle-income countries.
[a] Frequencies of positive responses are presented as cumulative percentages within each time interval using the total of responses from each income category as a denominator and applying post-stratification correction by hospital and country.

Table 4
Antibiotic compounds always prescribed in combination by respondents

Prescribing frequency	I prescribe combination very rarely	Meropenem/vaborbactam	Ceftazidime/avibactam	Ceftolozane/tazobactam	Plazomicin	Eravacycline	Aztreonam
	N (%)	C/A (%)	C/A (%)	C/A (%)	C/A (%)	C/A (%)	C/A (%)
High-rate prescriber	11/255 (4.3)	0/4 (0.0)	39/86 (45.3)	26/93 (28.0)	1/3 (33.3)	0/2 (0.0)	28/100 (28.0)
Medium-rate prescriber	29/321 (9.0)	7/19 (36.8)	72/146 (49.3)	47/151 (31.1)	0/3 (0.0)	0/4 (0.0)	37/139 (26.6)
Low-rate prescriber	68/209 (32.5)	4/23 (17.4)	34/101 (33.7)	21/100 (21.0)	2/6 (33.3)	2/6 (33.3)	24/117 (20.5)
Overall	108/785 (13.7)	11/46 (23.9)	145/333 (45.3)	94/344 (27.3)	3/12 (25)	2/12 (16.7)	89/356 (25)
p value	<0.001	NP	0.047	NP	NP	NP	NP
Prescribing frequency	**Gentamicin**	**Tobramycin**	**Amikacin**	**Tigecycline**	**Polymyxin B**	**Colistin**	**Fosfomycin (IV)**
	C/A (%)	**C/A (%)**	**C/A (%)**	**C/A (%)**	**C/A (%)**	**C/A (%)**	**C/A (%)**
High-rate prescriber	81/250 (32.4)	17/132 (12.9)	119/248 (48.0)	132/228 (57.9)	45/99 (45.5)	191/230 (83.0)	98/162 (60.5)
Medium-rate prescriber	109/315 (34.6)	26/176 (14.8)	173/307 (56.4)	61/263 (23.2)	41/121 (33.9)	212/281 (75.4)	105/188 (55.9)
Low-rate prescriber	74/205 (36.1)	37/137 (27.0)	102/187 (54.5)	137/156 (87.8)	18/77 (23.4)	89/160 (55.6)	41/113 (36.3)
Overall	264/770 (34.2)	80/445 (17.9)	394/742 (53)	330/647 (70.6)	104/297 (35)	492/671 (73)	244/463 (52.7)
p value	NP	0.004	NP	<0.001	0.009	<0.001	<0.001

Abbreviations: A, number of respondents with available agent; C, always in combination; IV, intravenous; NP, not performed (fewer than five respondents contributed to the analysis).
The results are presented as proportions and stratified by prescribing frequency. As denominator, only the number of respondents declaring the availability of the antibiotic compounds was considered. The statistical significance was computed only if more than five respondents contributed to the analysis.

commonly prescribed treatment among children was 'carbapenem plus polymyxin'. Full data on paediatric populations are available in the Supplementary material (Tables S14–S16).

The concept of 'combination therapy'

The main reasons leading to the prescription of combination treatment were to improve clinical efficacy (570/707; 81% of respondents) and to reduce resistance development (364/707; 51%) (see Supplementary material, Fig. S5). According to 80% of respondents (611/783), 'combination therapy' must include antibiotics that retain some degree of *in vitro* activity (321/783; 42% of respondents) or be synergic (290/783; 38% of respondents). Twenty per cent of respondents (150/783) conceived 'combination therapy' as the simple association of two or more antibiotic compounds, regardless of their potential *in vitro* activity (see Supplementary material, Table S17).

Type of evidence supporting the use of combination therapy included: experts' recommendations (62%; 486/777), evidence from randomized controlled trials (37%; 285/777), evidence from *in vitro* studies (36%; 277/777), controlled observational studies (34%; 264/777) and personal experience (29%; 224/777) (see Supplementary material, Fig. S6).

Discussion

Our results showed that the treatment of CR-GNB infections is far from being standardized and clinicians across the world use a

Please cite this article as: Carrara E et al., Clinical management of severe infections caused by carbapenem-resistant gram-negative bacteria: a worldwide cross-sectional survey addressing the use of antibiotic combinations, Clinical Microbiology and Infection, https://doi.org/10.1016/j.cmi.2021.05.002

(%) OF RESPONDENTS			CLINICAL FACTORS			
			Clinically stable/ No risk factor for immunodepression	Clinically stable/ Risk factors for immunodepression	Worsening clinical conditions (empirical therapy not covering CR-GNB)	Septic shock
EPIDEMIOLOGICAL/MICROBIOLOGICAL FACTORS	Known colonization in ANY site	HIC	8·1	32·7	80·6	70·2
		UMIC	4·3	26·4	66·6	63·4
		LMIC/LIC	2·3	35·5	50·1	43·7
		p value	NS	NS	0·003	0·02
	The Infection originates from a known colonized site	HIC	28·0	55·0	83·1	67·9
		UMIC	14·8	46·9	74·1	62·8
		LMIC/LIC	26·9	36·0	40·6	42·6
		p value	NS	NS	< 0·001	0·03
	Recent admission in a highly-endemic hospital (<90 days)	HIC	7·6	64·3	67·2	66·8
		UMIC	6·3	29·8	65·7	62·7
		LMIC/LIC	6·0	38·7	49·1	36·4
		p value	NS	NS	NS	0·005
	Recent travel in a highly-endemic country (<90 days)	HIC	4·7	26·2	58·7	57·1
		UMIC	4·6	18·3	62·1	58·7
		LMIC/LIC	9·3	18·2	43·7	31·1
		p value	NS	NS	NS	0·01
	Recent exposure to carbapenem (<90 days)	HIC	5·9	23·0	56·0	55·3
		UMIC	5·4	27·2	66·4	50·1
		LMIC/LIC	3·9	15·8	44·0	61·3
		p value	NS	NS	NS	NS
	Preliminary identification highly suggestive of CR-GNB	HIC	25·6	60·5	81·0	70·5
		UMIC	24·8	45·9	81·2	70·9
		LMIC/LIC	13·2	46·7	58·0	41·0
		p value	NS	NS	0·006	0·003
	Positive rapid susceptibility tests i.e. NAAT, carba-NP*	HIC	54·6	68·3	63·5	62·7
		UMIC	30·9	53·6	67·4	65·5
		LMIC/LIC	0·0	30·4	69·5	54·3
		p value	NS	NS	NS	NS

Abbreviations: HIC: high income countries; UMIC: upper-middle income countries; LMIC: lower-middle income countries; LIC: low income countries; NAAT: nucleic acid amplification testing; NS: not statistically significant.
*Number of respondents for denominator are 215 (only the respondents declaring that their labs can perform rapid tests for CR-GNB).
The results are presented as weighted proportions after adopting post-stratification correction according to hospital and country. The likelihood of empiric coverage for CR-GNB is divided into four thresholds and graphically represented according to this color scale: < 15% | 15-30% | 31-50% | > 50%

Fig. 1. Percentage of respondents who are likely to cover empirically for carbapenem-resistant Gram-negative bacteria according to different clinical, epidemiological/microbiological factors and stratified by country–income.

wide range of antibiotic strategies and combinations depending on clinical severity, local availability and clinical experience. Of interest, empiric coverage for CR-GNB was driven mostly by the severity of the clinical scenario and was more commonly prescribed in high-income countries compared with less resourced settings. As for targeted treatment, the majority of respondents opted for a double-antibiotic combination (most commonly polymyxin plus carbapenem) despite the lack of evidence supporting this indication.

Access to rapid diagnostics and recently approved antibiotics was inversely correlated with country economic status. Gentamicin, amikacin and trimethoprim-sulfamethoxazole were the most accessible compounds worldwide, whereas new β-lactam/β-lactamase inhibitors and also older antibiotics such as colistin and polymyxin B were available in less than 50% of the surveyed countries. Our results confirmed that it is not only high-priced newer drugs that are very rarely accessible, but also off-patent drugs can encounter supply shortages because manufacturing costs are not compensated by the low sale-price [19]. A survey conducted by the European Society of Clinical Microbiology and Infectious Diseases revealed that there was a reduction in access to 'old antibiotics' in the USA, Europe and Australia from 2011 to 2015 [20]. Similar data collected in lower-middle-income countries found that access to 'old antibiotics' was very limited, even in countries with high rates of antibiotic resistance [21].

Please cite this article as: Carrara E et al., Clinical management of severe infections caused by carbapenem-resistant gram-negative bacteria: a worldwide cross-sectional survey addressing the use of antibiotic combinations, Clinical Microbiology and Infection, https://doi.org/10.1016/j.cmi.2021.05.002

Up to 80% of respondents from high-income countries favoured empirical coverage for CR-GNB in presence of severe clinical condition and epidemiological risk factors. Conversely, confronted with the same clinical scenario, only half of respondents from lower-middle-income countries/lower-income countries opted for empirical coverage of CR-GNB. The main reason for this significant discrepancy probably resides in the lack of viable therapeutic options in those countries, in line with the most recent findings revealing that early coverage with colistin does not provide any benefit on survival in presence of severe CR-GNB infections [22].

As for targeted treatment, despite the overall preference for dual antibiotic therapy, a notable portion of prescribers still opt for monotherapy when dealing with microbiologically documented CR-GNB infections. The choice of monotherapy could either reflect the actual lack of evidence supporting specific combinations or the absence of other viable options due to concomitant resistance, drug toxicity or local unavailability.

Despite the relatively low percentage of paediatricians and neonatologists contributing to the survey (8.5%), a significant heterogeneity of prescribing patterns was also identified in this patient population. A similar lack of standardization has already been observed in two global point prevalence surveys, where almost 200 different antibiotic regimens were used for treating sepsis in children and neonates [23,24].

Overall, 80% of prescribers agreed that the main aim of combination therapy is to improve therapeutic efficacy, while 50% supported the use of combination therapy for reducing resistance development or promoting microbe eradication when compared with monotherapy. The majority of prescribers seemed to recognize that the use of combination therapy for treating CR-GNB infections comes from 'expert' recommendations and that the supporting evidence is very poor and of low quality, being composed almost exclusively of observational and *in vitro* studies. Interestingly, approximately one-third of respondents believed that the use of combination therapy is supported by randomized controlled trials, although valid examples in the literature are scarce [25]. A much higher rate of prescribers sharing this same misconception was also observed in a similar survey on management of CR-GNB infections in Europe and the USA in 2017; in that study, up to 55% of respondents declared that combination therapy was supported by a strong level of evidence [26].

Finally, it is notable that the concept of 'combination therapy' had a different meaning among respondents, with 42% indicating 'combination of *in vitro* active drugs', 38% indicating 'combination of *in vitro* synergistic drugs' and 20% indicating 'combination of two or more drugs, regardless of the *in vitro* activity'. Disagreement among respondents clearly reflects the lack of a standardized definition for 'combination therapy' also in clinical studies, with the result that there can be a misinterpretation and poor generalizability of study results [27].

Although the referral process allowed the rapid recruitment of respondents from areas of the world that are usually difficult to access, the use of a non-probabilistic sampling method remains a main limitation of this study. Our sampling process started from surveillance networks to track and filter hospitals and countries with the minimum standard needed for diagnosing CR-GNB infections. Therefore, we may have missed countries and hospitals in which microbiological diagnosis is made with an acceptable degree of standardization, but without active surveillance systems, particularly in lower-middle-income countries/lower-income countries and non-English speaking countries. Additionally, it should be considered that individuals embedded in a network have greater probabilities of being identified and accessed than others, with the risk of over-representing certain prescribers. For this reason, a post-stratification correction with inverse proportional weighting was applied to mitigate the risk of oversampled countries and hospitals.

In conclusion, we recorded a huge variability in the management of severe CR-GNB infections among over 1000 clinicians worldwide. Unequal access to diagnostic and therapeutic resources and the unavailability of evidence-based recommendations were two strong determinants contributing to this heterogeneity. Additionally, the lack of a universally accepted definition of 'combination therapy' might have further impaired the confidence in results from available clinical studies. These results demonstrate the urgent need for public-health-focused strategic randomized controlled trials with the involvement of low-income and low-to middle-income countries. International guidelines will be able to inform decision-making only when results from adequately conducted randomized controlled trials become available.

Author contributions

ET and LJVP conceived the idea for this project. EC, AS, SE, FF, LJVP and ET designed the study. AS, EC and AG contributed to the data analysis and synthesis. AS and EC wrote the paper. All authors contributed to the survey development, pilot phase, revision of the paper and approval of the final version for submission. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Transparency declaration

AS, EC, AG, GLH, ER, CT, AR, HZ, CG, AJB and ET have no competing interests to be declared. SE, FF and LJVP are employed by GARDP. PNAH declares research grants outside the submitted work from Sandoz, Shionogi and MSD and speakers' fees from Pfizer.

Role of the funding source

GARDP supported the entire project, GARDP secondee (LJVP) and employees contributed to study design, data interpretation and writing of the manuscript. All authors had full access to data and had final responsibility for the decision to submit for publication.

Acknowledgements

We thank Ruth Joanna Davis for the editorial support. We also thank each member of the COHERENCE core-expert group: Mohammad Abdallah, Aaron Oladipo Aboderin, Akim Adegnika Ayola, Tara Anderson, Anucha Apisarnthanarak, Tobias Manuel Appel, Amin A. Aqel, Alexandra Barac, Nur Benzonana, Gabriel Birgand, Michael Borg, Eric Brown, Biljana Carević, Miquel Ekkelkamp, Karl Emerole, Maha Fathy, Fidelma Fitzpatrick, Nikkiah Forbes, Corey A. Forde, Alexander W. Friedrich, Ana Cristina Gales, Brent Gilpin, Christian Giske, Debra Goff, Eduardo Gotuzzo, Nelesh Govender, Manuel Guzman Blanco, Rahm Hamers, Patrick Harris, Po-Ren Hsueh, Alain C. Juayan, Gunnar Kahlmeter, Souha Kanj, Basudha Khanal, Yang Soo Kim, Bela Kocsis, Roman Kozlov, Fiorella Krapp Lopez, Jaime Labarca, Todd Campbell Lee, Amel Omezzine Letaief, Gabriel Levy Hara, Yi-Tsung Lin, Veranja Liyanapathirana, David Lupande, Surbhi Malhotra-Kumar, Kalisvar Marimuthu, Marc Mendelson, Gordana Mijovic, Rima A. Moghnieh, Andreea Moldovan, Jaime C. Montoya, Nico Mutters, Lawrence Mwananyanda, Aissatou Lakhe Ndeye, Jason Newland, Alison Nicholson, Ahmad Norazah Binti, Carlos Palos, Lea Papst, Aurelia Jennifer Perera, Pakpoom Phoompoung, Chimanjita Phukan, Elisabeth Presterl, Dianelys Quinones Perez, Lul Raka, Ossama Rasslan, Elda Righi, Jesus Rodriguez Bano, Emmanuel Roilides, Bhattacharya Sanjay, Al-Abri Seif Salem, Sharmila Sengupta, Sadia Shakoor, Mike Sharland, Nalini Singh, Le Huu Song, Igor Stoma, Silva Tafaj, Pierre Tattevin, Jens Thomsen, Athanasios Tsakris, David Tsibadze, Paul Turner, David Van Duin,

Please cite this article as: Carrara E et al., Clinical management of severe infections caused by carbapenem-resistant gram-negative bacteria: a worldwide cross-sectional survey addressing the use of antibiotic combinations, Clinical Microbiology and Infection, https://doi.org/10.1016/j.cmi.2021.05.002

Silvio Vega, Thirumalaisamy P Velavan, Aija Vilde, Maria Virginia Villegas, Peter Waiswa, Timothy Walsh, Minggui Wang, Evelyn Wesangula, Andreas F. Widmer, Yonghong Xiao, Wei Yu, Hiba Zayyad, Benedetta Allegranzi, Anna Zorzet.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2021.05.002.

References

[1] Tacconelli E, Carrara E, Savoldi A, Harbarth S, Mendelson M, Monnet DL, et al. Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. Lancet Infect Dis 2018;18:318–27.
[2] Theuretzbacher U, Bush K, Harbarth S, Paul M, Rex JH, Tacconelli E, et al. Critical analysis of antibacterial agents in clinical development. Nat Rev Microbiol 2020;18:286–98.
[3] Parchem NL, Bauer KA, Cook CH, Mangino JE, Jones CD, Porter K, et al. Colistin combination therapy improves microbiologic cure in critically ill patients with multi-drug resistant gram-negative pneumonia. Eur J Clin Microbiol Infect Dis 2016;35:1433–9.
[4] Simsek F, Gedik H, Yildirmak MT, Iris NE, Turkmen A, Ersoy A, et al. Colistin against colistin-only-susceptible *Acinetobacter baumannii*-related infections: monotherapy or combination therapy? Indian J Med Microbiol 2012;30:448–52.
[5] Qureshi ZA, Paterson DL, Potoski BA, Kilayko MC, Sandovsky G, Sordillo E, et al. Treatment outcome of bacteremia due to KPC-producing *Klebsiella pneumoniae*: superiority of combination antimicrobial regimens. Antimicrob Agents Chemother 2012;56:2108–13.
[6] Hawkey PM, Warren RE, Livermore DM, McNulty CAM, Enoch DA, Otter JA, et al. Treatment of infections caused by multidrug-resistant gram-negative bacteria: report of the British society for antimicrobial chemotherapy/healthcare infection society/British infection association joint working party. J Antimicrob Chemother 2018;73. iii2–iii78.
[7] Rodriguez-Bano J, Gutierrez-Gutierrez B, Machuca I, Pascual A. Treatment of infections caused by extended-spectrum-beta-lactamase-, ampc-, and carbapenemase-producing *Enterobacteriaceae*. Clin Microbiol Rev 2018;31.
[8] Isler B, Doi Y, Bonomo RA, Paterson DL. New treatment options against carbapenem-resistant *Acinetobacter baumannii* infections. Antimicrob Agents Chemother 2019;63.
[9] Sadler GR, Lee HC, Lim RS, Fullerton J. Recruitment of hard-to-reach population subgroups via adaptations of the snowball sampling strategy. Nurs Health Sci 2010;12:369–74.
[10] Naderifar MGH, Ghaljaie F. Snowball sampling: a purposeful method of sampling in qualitative research. Strides Dev Med Educ 2017;14(3):e67670.
[11] Atkinson RFJ. Accessing hidden and hard-to-reach populations: snowball research strategies. Social research UPDATE. Department of Sociology University of Surrey; 2001.
[12] Colbert CY, Diaz-Guzman E, Myers JD, Arroliga AC. How to interpret surveys in medical research: a practical approach. Cleve Clin J Med 2013;80:423–35.
[13] Kelley K, Clark B, Brown V, Sitzia J. Good practice in the conduct and reporting of survey research. Int J Qual Health Care 2003;15:261–6.
[14] Bennett C, Khangura S, Brehaut JC, Graham ID, Moher D, Potter BK, et al. Reporting guidelines for survey research: an analysis of published guidance and reporting practices. PLoS Med 2010;8:e1001069.
[15] Burns KE, Duffett M, Kho ME, Meade MO, Adhikari NK, Sinuff T, et al. A guide for the design and conduct of self-administered surveys of clinicians. CMAJ 2008;179:245–52.
[16] Draugalis JR, Coons SJ, Plaza CM. Best practices for survey research reports: a synopsis for authors and reviewers. Am J Pharm Educ 2008;72:11.
[17] Little RJA. Post-stratification: a modeler's perspective. J Am Stat Assoc 1993;88:1001–12.
[18] Williams R. Post-stratification and response bias in survey data with applications in political science. Computer Science; 2005.
[19] Monnier AA, Schouten J, Tebano G, Zanichelli V, Huttner BD, Pulcini C, et al. Ensuring antibiotic development, equitable availability, and responsible use of effective antibiotics: recommendations for multisectoral action. Clin Infect Dis 2019;68:1952–9.
[20] Pulcini C, Mohrs S, Beovic B, Gyssens I, Theuretzbacher U, Cars O. Forgotten antibiotics: a follow-up inventory study in Europe, the USA, Canada and Australia. Int J Antimicrob Agents 2017;49:98–101.
[21] Tebano G, Li G, Beovic B, Bielicki J, Brink A, Enani MA, et al. Essential and forgotten antibiotics: an inventory in low- and middle-income countries. Int J Antimicrob Agents 2019;54:273–82.
[22] Zak-Doron Y, Dishon Benattar Y, Pfeffer I, Daikos GL, Skiada A, Antoniadou A, et al. The association between empirical antibiotic treatment and mortality in severe infections caused by carbapenem-resistant Gram-negative bacteria: a prospective study. Clin Infect Dis 2018;67:1815–23.
[23] Logan LK, Renschler JP, Gandra S, Weinstein RA, Laxminarayan R. Carbapenem-resistant *Enterobacteriaceae* in children, United States, 1999–2012. Emerg Infect Dis 2015;21:2014–21.
[24] Jackson C, Hsia Y, Basmaci R, Bielicki J, Heath PT, Versporten A, et al. Global divergence from World Health Organization treatment guidelines for neonatal and pediatric sepsis. Pediatr Infect Dis J 2019;38.
[25] Paul M, Daikos GL, Durante-Mangoni E, Yahav D, Carmeli Y, Benattar YD, et al. Colistin alone versus colistin plus meropenem for treatment of severe infections caused by carbapenem-resistant Gram-negative bacteria: an open-label, randomised controlled trial. Lancet Infect Dis 2018;18:391–400.
[26] Papst L, Beovic B, Pulcini C, Durante-Mangoni E, Rodriguez-Bano J, Kaye KS, 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. Clin Microbiol Infect 2018;24:1070–6.
[27] 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.

Please cite this article as: Carrara E et al., Clinical management of severe infections caused by carbapenem-resistant gram-negative bacteria: a worldwide cross-sectional survey addressing the use of antibiotic combinations, Clinical Microbiology and Infection, https://doi.org/10.1016/j.cmi.2021.05.002