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Global prevalence of carbapenem resistance in neutropenic patients and association with mortality and carbapenem use: systematic review and meta-analysis

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Background: Carbapenem-resistant Gram-negative bacteria are recognized as a cause of difficult-to-treat infections associated with high mortality.

Objectives: To perform a systematic review of currently available data on distribution, characteristics and outcome associated with carbapenem-resistant bloodstream infections in adult neutropenic patients.

Methods: Included studies were identified through Medline, Embase and Cochrane databases between January 1995 and April 2016. Random effect meta-analysis was used to quantify the association between carbapenem resistance and mortality and between carbapenem exposure and resistance.

Results: A total of 30 studies from 21 countries were included. Overall carbapenem resistance varied from 2% to 53% (median 9%) among studies. Infections due to carbapenem-resistant *Pseudomonas* spp. were reported in 18 (60%) studies showing high median resistance rates (44% of all carbapenem-resistant Gram-negatives and 19% of *Pseudomonas* isolates). Resistance of Enterobacteriaceae was less commonly reported and bloodstream infections due to carbapenem-resistant *Klebsiella* spp. were mainly documented from endemic areas (Greece, Italy, Israel). Carbapenem resistance in *Acinetobacter* spp. was reported in 9 (30%) studies (median resistance 58% of *Acinetobacter* isolates). Mortality rates ranged from 33% to 71% (median 50%) in patients with carbapenem-resistant infections. Carbapenem resistance appeared to correlate with mortality (OR 4.89, 95% CI 3.30–7.26) and previous exposure to carbapenems (OR 4.63, 95% CI 3.08–6.96).

Conclusions: Carbapenem resistance represents a threat to neutropenic patients. In this group, resistance is likely promoted by previous carbapenem use and leads to high mortality rates. The knowledge of resistance patterns is crucial and can direct clinicians in the use of alternatives to carbapenem-based regimens.

Introduction

Bloodstream infections (BSIs) are common among cancer patients, showing prevalence rates ranging from 11% to 38% and crude mortality rates up to 40%.[1] In these patients, the excessive and prolonged use of broad-spectrum antibiotics during febrile neutropenic episodes is a crucial factor for the colonization of various body sites by MDR Gram-negative bacteria (GNB).[2] The increasing prevalence of MDR GNB such as ESBL-producing organisms and carbapenem-resistant (CR) bacteria has limited the choice of effective antimicrobials, representing one of the biggest challenges in treating immunocompromised patients in recent years.[3]

Carbapenems, in particular, often represent the last resort for treating MDR GNB. Early use of a carbapenem (meropenem or imipenem/cilastatin) in febrile neutropenia is recommended for high-risk patients (i.e. absolute neutrophil count <100 cells/mm^3 for >7 days and/or significant comorbidities, or haemodynamically unstable patients), in case of previous infection or colonization with ESBL-producing bacteria or in hospitals with high ESBL rates.[4,5] As

a consequence, the use of carbapenems in neutropenic patients has greatly increased, likely contributing to the rise of CR infections. Furthermore, in this patient population an increase in infections caused by GNB, especially those prone to accumulate multiple antibiotic resistances (e.g. *Pseudomonas aeruginosa* and *Acinetobacter baumannii*), has been reported.[6]

A paucity of multicentre prospective studies on antimicrobial resistance, however, currently limits the knowledge of carbapenem resistance prevalence and its impact on mortality among neutropenic patients.

The aim of this systematic review was to examine currently available data on the distribution, characteristics and outcome of BSIs caused by CR GNB in adult neutropenic patients.

Methods

This study was conducted in accordance with the PRISMA guidelines as described below.[7]

Search strategy and selection criteria

This review is registered with the PROSPERO international prospective register of systematic reviews (CRD42016038278, www.crd.york.ac.uk/PROSPERO/). We searched Medline, Embase and Cochrane databases for publications in any language between 1995 and April 2016 documenting carbapenem resistance in adult neutropenic patients with BSIs. All search strings were discussed with a qualified librarian. Details of the bibliographic search strategy are listed in Appendix S1 (available as Supplementary data at *JAC* Online). Bibliographies of reviews and original publications were hand searched for further studies. An additional search was performed in Google Scholar with the same search criteria as that applied to the electronic databases. We also searched BASE (Bielefeld Academic Search Engine), ProQuest, ETHOS (Electronic Theses Online Service), OpenDOAR and Clinical Key for conference proceedings, national reports, open access material and abstracts that may not have been indexed in these databases.

Data extraction

Any type of study, except case reports, was considered. Two investigators (E. R. and A. M. P.) independently assessed each potentially relevant study for eligibility. Disagreements were resolved by consultation with a third party (P. N. A. H.). If eligibility could not be determined, the full article was retrieved. Publications reporting original data on carbapenem resistance in adult patients (18 years of age and older) with neutropenia and BSIs were included. Bacterial isolates were considered resistant to carbapenems according to the local interpretive criteria. A standardized data-extraction method was used to record relevant features of each study into a database, including: study characteristics (year of publication, recruitment time period, country, study design, number of BSIs, bacteria cultured, reported antibiotic susceptibilities), patient demographics (age, sex, definition and duration of neutropenia, underlying disease), method of antimicrobial susceptibility testing and antimicrobial therapy. Outcomes assessed included carbapenem resistance prevalence, previous carbapenem exposure as a variable associated with carbapenem resistance, and mortality related to CR infections. Studies that did not allow data retrieval on carbapenem resistance in neutropenic patients or from BSIs, as well as paediatric studies, were excluded.

Quality assessment

The Cochrane collaboration's risk of bias tool was used to assess papers for quality.[8] Selection bias was assessed with the Critical Appraisal Skills Programme (CASP) checklist for cohort and case–control studies (www.casp-uk.net). Quality assessment charts were produced identifying 'good', 'adequate' and 'poor' reporting (Appendix S2). Key quality criteria for eligible studies included: a reliable measure of antibiotic resistance, clear reporting of carbapenem resistance and BSIs. The same quality indicators were applied for papers that included information on mortality and previous carbapenem exposure. We intended to perform adjustment for confounders of mortality (e.g. age, sex, comorbidities) but only a few eligible studies reported patient-level data on these characteristics.

Data analysis

Analyses were conducted using SPSS version 24.0 software (SPSS Inc., Chicago, IL, USA) and MetaXL version 5.0 (EpiGear International). Studies comparing mortality and previous carbapenem exposure between CR and carbapenem-susceptible (CS) bacteria were included in the meta-analysis. The time to follow-up was taken as defined by each individual study and 30 day mortality was used as the primary outcome where several follow-up times were reported.

ORs with 95% CI for mortality were calculated between CR and CS BSIs, and ORs with 95% CI for carbapenem exposure as a variable associated with carbapenem resistance were calculated between patients with CR and CS infections or, in one study, between CR and other Gram-negative BSIs. Because of the differences that were expected between studies, the results were combined using a random effects model.[9] Heterogeneity between studies was assessed using the χ^2 ($P < 0.01$ suggesting significant heterogeneity) and I^2 tests (0%–40% no heterogeneity, 30%–60% moderate, 50%–90% substantial and 75%–100% considerable heterogeneity).[10] Funnel plots were generated to explore the possibility of small study effects, which can be caused by publication bias, and are reported in Appendix S3.

Results

Study characteristics

A total of 1699 citations were revealed by the literature searches. From these, 185 articles were retrieved for further scrutiny and 30 met the inclusion criteria (Figure 1).[11–40] Only one disagreement concerning the study design occurred for a conference abstract that was ultimately excluded from the review. No grey literature or national reports were eligible for inclusion in the review. All studies included were observational and most were retrospective (Table 1). Twenty-eight reported information on prevalence of carbapenem resistance among GNB; two articles did not analyse CR prevalence but reported data on factors and/or outcome associated with CR infections.[11,22] Additional characteristics of the included studies are reported in Appendix S4. Neutropenia was defined by the majority of studies as an absolute neutrophil count (ANC) below 500/mm^3. Eight studies reported neutropenia as ANC $<$1000/mm^3 (with predicted decrease below 500 within 48–72 h),[14,17–20] and two studies as ANC $<$1000/mm^3.[38,39] Duration of neutropenia was reported by nine studies.[11,14,16,19,27,29,35,36,39] Haematological malignancies represented the main cause of neutropenia; seven studies included also patients with solid cancer (ranging from 5% to 44% of the patient population). Acute leukaemia was the most common haematological disease in 17 (57%) studies. The origin of BSIs was nosocomial in the vast majority of cases (>90%). GNB BSIs ranged from 22% to 74% (median rate 52%), while the number of GNB among all isolates varied from 17% to 78% (median rate 51%). GNB were more common than Gram-positive bacteria in 10 out of

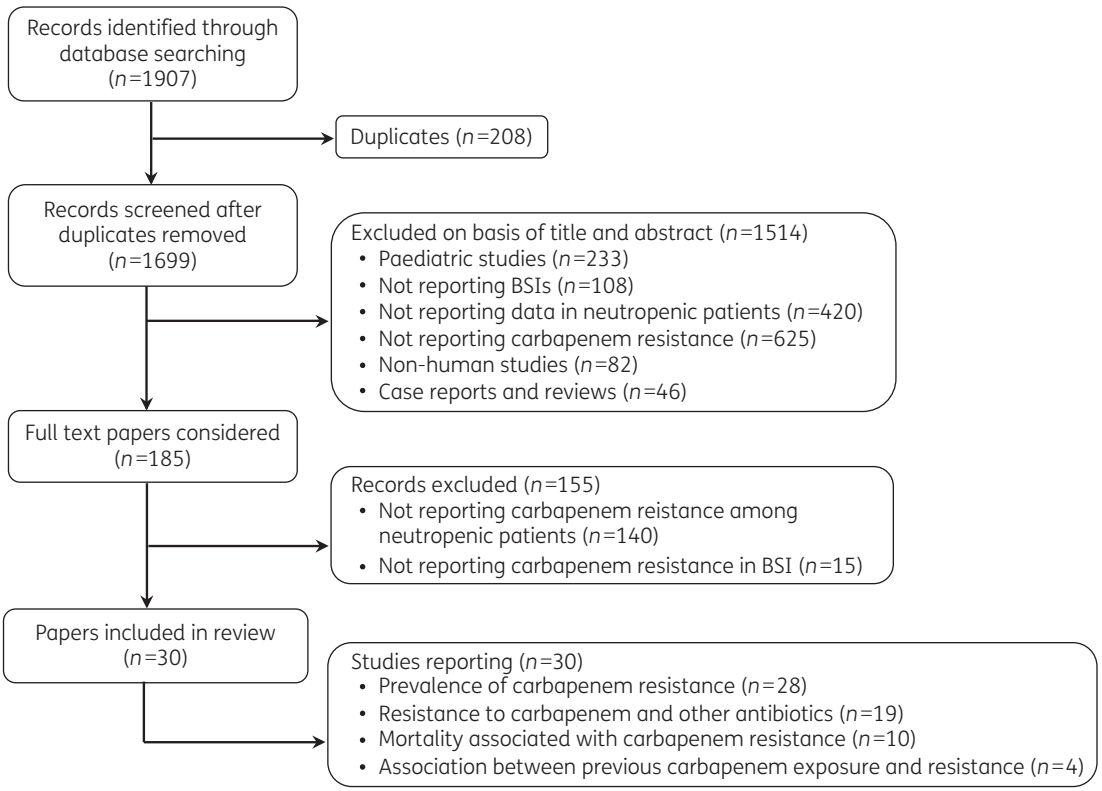

Figure 1. Data search and extraction (PRISMA flow chart).

17 (59%) studies reporting GNB BSIs and in 13 out of 23 (57%) reporting the total number of GNB isolates. *Escherichia coli* (35%, range 4%–61%), *Klebsiella* spp. (19%, range 0%–40%) and *Pseudomonas* spp. (14%, range 0%–40%) were the most common isolated strains among GNB.

Antimicrobial susceptibility testing was documented according to the CLSI in 16 studies[12,14,17,18,22,23,25,28,31–33,35–38,40] and according to EUCAST or to Swedish Reference Group for Antibiotics (SRGA) breakpoints in two studies,[11,21] while for the others the testing method was not documented. Only two reports performed molecular characterization of CR strains.[11,32]

Distribution of carbapenem resistance

Data were collected from various geographic areas: 16 studies were conducted in Europe, North Africa and the Middle East, 10 in Asia, 3 in Central and South America, and 1 in South Africa. As summarized in Table 2, CR rates varied widely across the studies, ranging from 2% to 33% (median 12%) among BSIs and from 2% to 53% (median 9%) among all GNB (data available from 14 and 25 studies, respectively). Figure 2 shows the pooled prevalence (or single-study reported prevalence if $n = 1$) of CR GNB bacteria by country. The number of reports addressing the issue of CR GNB increased over time, especially during the past decade. Only 5 papers were published between 1995 and 2005 compared with 11 during 2006–10 and 14 during 2011–16.

The prevalence of CR *Pseudomonas* spp. was reported in 18 (60%) studies and ranged from 6% to 100% (median 19%) among *Pseudomonas* strains and from 11% to 100% (median 44%) among all GNB. Carbapenem resistance >10% among isolated *Pseudomonas* was reported in 14 out of 17 (82%) studies. Only four recent studies, two from Italy, one from Turkey and one from Israel, reported the occurrence of CR *Klebsiella pneumoniae* (CR-Kp); resistance rates were 35%, 14%, 7% and 46% of all *Klebsiella* spp. isolates, respectively (Table 2).[13–15,30] CR was, instead, less commonly reported among other Enterobacteriaceae such as *E. coli* and *Enterobacter* spp. (Table 2). Nine (30%) studies identified carbapenem resistance in *Acinetobacter* spp., highlighting high median resistance rates (58%, range 13%–100% of all *Acinetobacter* isolates).

Few studies reported resistance data for other antimicrobials among GNB (Appendix S5). The majority of the studies highlighted higher rates of resistance to antimicrobials often used as prophylaxis or empirical therapy (e.g. fluoroquinolones, piperacillin/tazobactam and cephalosporins) compared with carbapenems (Figure 3). A report from Turkey, however, documented higher percentages of CR compared with ESBL-producing bacteria (23% versus 15%, respectively).[19] Compared with other GNB, *P. aeruginosa* maintained consistently high levels of carbapenem resistance (Figure 3). A Swedish study showed higher resistance rates for imipenem compared with other antibiotics tested against *P. aeruginosa*.[21]

Variables associated with the acquisition of carbapenem resistance

Only a few studies analysed duration of neutropenia,[40] disease type or severity[13,14] as factors associated with carbapenem

Table 1. Characteristics of included studies

Reference	Period	Country	Study type	Number of BSIs (GNB %)	GNB (% of isolates)	*E. coli*, *Klebsiella* spp., *Pseudomonas* spp. (% of GNB)
Tofas *et al.*[11]	2010–14	Greece	retrospective	50 (100)	50 (100)	0, 100, 0[a]
Alshukairi *et al.*[12]	2011–12	Saudi Arabia	retrospective	75 (NR)	48/78 (62)	35, 23, 13
Andria *et al.*[13]	2008–14	Israel	retrospective	423 (100)	100	33, 24, 20
Kara *et al.*[14]	2005–09	Turkey	retrospective	536 (60)	NR	33, 25, 13
Trecarichi *et al.*[15]	2009–12	Italy	prospective	575 (46)	353/668 (53)	53, 12, 19
Kikuchi *et al.*[16]	2006–13	Japan	retrospective	130 (24)	31/130 (24)	10, NR, 23
Moghnieh *et al.*[17]	2009–12	Lebanon	retrospective	75 (57)	43/75 (57)	40, 26, 12
El-Mahallawy *et al.*[18]	2009	Egypt	retrospective	39 (67)	26/39 (67)	4, 12, 19
Gedik *et al.*[19]	2010–12	Turkey	retrospective	66 (74)	49/66 (74)	35, 27, 14
Kwon *et al.*[20]	2009–10	South Korea	retrospective	222 (NR)	119/243 (49)	61, 26, 4
Kjellander *et al.*[21]	1995–2008	Sweden	retrospective	667 (NR)	372/794 (47)	38, 21, 11
Mudau *et al.*[22]	2010–11	South Africa	case–control	36 (100)	NR	NR, NR, 28
Huang *et al.*[23]	2003–05	Taiwan	retrospective	275 (72)	263/340 (77)	22, 17, 14
Han *et al.*[24]	2008–10	China	retrospective	75 (64)	47/94 (50)	47, 10, 0
Chen *et al.*[25]	2002–06	Taiwan	retrospective	NR	516/853 (60)	20, 17, 9
Jin *et al.*[26]	2008–09	Singapore	prospective	49 (51)	25/49 (51)	44, 40, 12
Jeddi *et al.*[27]	2007	Tunisia	prospective	27 (48)	13/27 (48)	8, 38, 8
Suárez *et al.*[28]	2005	Spain	retrospective	12 (NR)	NR	0, 0, 100[b]
Garnica *et al.*[29]	1995–2005	Brazil	retrospective	123 (45)	56/123 (45)	23, 13, 27
Mikulska *et al.*[30]	2004–07	Italy	retrospective	168 (32)	68/182 (37)	37, 10, 26
Irfan *et al.*[31]	1999–2006	India	retrospective	1048 (NR)	442/1048 (42)	35, 12, 20
Kim *et al.*[32]	2001–05	South Korea	case–control	NR	NR	0, 0, 100[c]
Baskaran *et al.*[33]	2004	Malaysia	retrospective	50 (NR)	44/73 (60)	36, 26, 9
Oliveira *et al.*[34]	2004	Brazil	prospective	91 (37)	59/118 (50)	17, 19, 22
Paul *et al.*[35]	1988–2004	Israel	prospective	462 (55)	353/557 (63)	30, 17, 26
Solano *et al.*[36]	1999–2000	Spain	case–control	41 (22)	9/54 (17)	56, 0, 0
Wang *et al.*[37]	1999–2002	Taiwan	retrospective	371 (NR)	327/418 (78)	28, 19, 11
Fanci *et al.*[38]	1995–98	Italy	retrospective	152 (56)	87/172 (51)	26, NR, 40
Gaytan-Martinez *et al.*[39]	1997	Mexico	prospective	42 (52)	24/47 (51)	42,17, 8
Krcméry *et al.*[40]	1990–94	Slovak Republic	retrospective	81 (NR)	NR	0, 0, 100[b]

NR, not reported.
[a]Only isolates of CR-Kp were included in the study.
[b]Only *Pseudomonas* spp. isolates were considered in the study.
[c]Only *Acinetobacter* spp. isolates were considered in the study.

resistance. In one study, salvage therapy and non-autologous transplants were more frequent in CR compared with CS infections.[13] Four studies reported previous exposure to carbapenems as a variable associated with CR BSIs[13,17,22,32] (Table 3), although one study did not confirm the data in multivariate analysis.[22] Our meta-analysis showed an association between carbapenem resistance and previous exposure to carbapenems (OR 4.63, 95% CI 3.08–6.96) (Figure 4).

Antimicrobial therapy and outcome of CR infections

One study out of 11 detailing the antimicrobial prophylaxis received by neutropenic patients (Appendix S4) analysed the correlation between prophylaxis and development of resistance but did not evidence an increase in CR GNB.[36] Empirical therapy consisted mainly of piperacillin/tazobactam, cefoperazone/sulbactam or an antipseudomonal cephalosporin with or without a fluoroquinolone or an aminoglycoside. Carbapenems were used as first-line empirical treatment in three studies and as escalation therapy (e.g. in case of clinical deterioration, septic shock, breakthrough BSIs) in nine. In one study, the combination of piperacillin/tazobactam and colistin was identified as the preferred empirical regimen due to high rates (>50%) of CR *P. aeruginosa*.[27] Definitive treatment of CR BSIs was reported only in a few studies and included colistin alone or in combination with amikacin or rifampicin.[11,13,19,22]

Data on the outcome of CR BSIs in neutropenic patients were reported by 10 studies.[11,13,15–17,19,21,22,30,32] Mortality rates ranged from 33.3% to 71.4% (median rates 50%). One study reporting only carbapenemase-producing Kp (KPC-Kp) BSIs

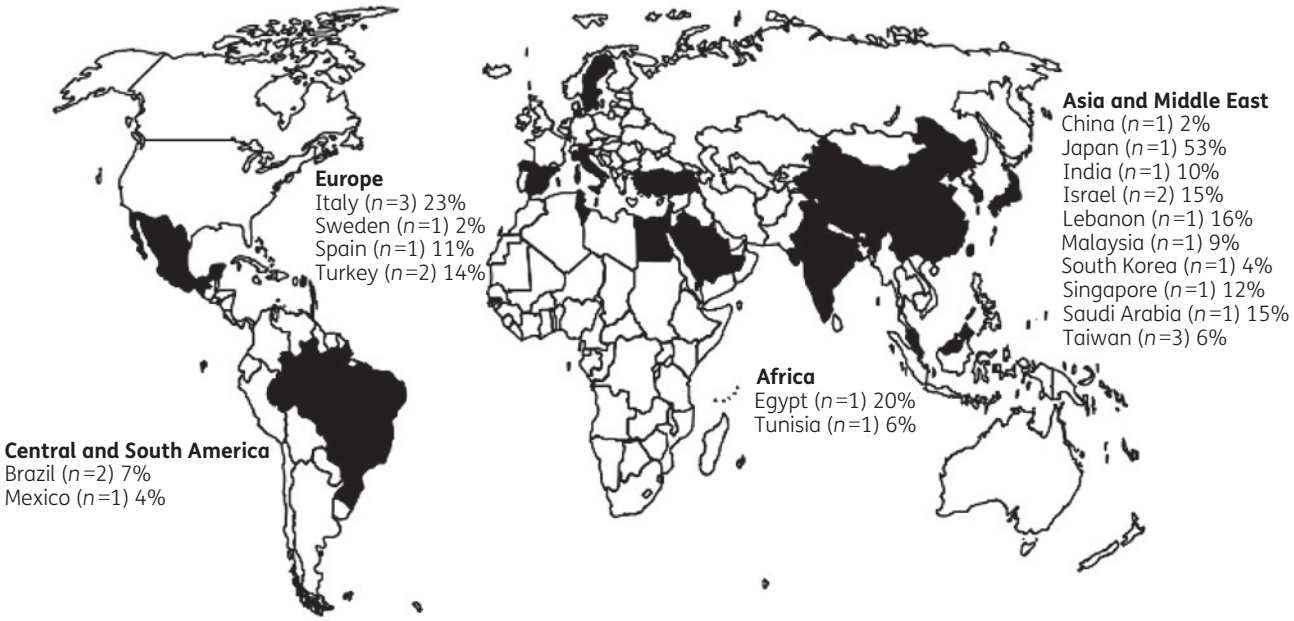

Figure 2. Geographical distribution of carbapenem resistance prevalence (%) in GNB isolated from BSIs in neutropenic patients, with number of included studies per country in parentheses.

identified lower mortality in patients receiving combination therapy with two or three active drugs compared with monotherapy (38% and 33% versus 50%, respectively).[11] Six studies compared mortality in CR versus CS strains;[13,15,17,19,21,32] among these, one large study reported OR adjusted for confounders (e.g. demographic data, comorbidities, type of haematological disease).[13] For these studies, our meta-analysis showed an association between mortality and carbapenem resistance (OR 4.89, 95% CI 3.30–7.26) (Figure 5).

Meta-analyses

We performed sensitivity analyses excluding one study each time and recalculating the combined results to investigate the influence of an individual dataset on the pooled OR. For both meta-analyses, the corresponding pooled ORs were not altered. ORs were also consistent with the reported results when *P. aeruginosa* was excluded from the analysis (OR 3.26, 95% CI 1.52–6.99); only recalculation for mortality and carbapenem resistance was possible for this analysis due to the lack of patient-level data on carbapenem use and carbapenem resistance (Appendix S6).

No heterogeneity was shown (Figures 4 and 5). To assess potential publication bias, results from meta-analyses were assessed using a funnel plot. Our funnel plots appeared asymmetrical (Appendix S3), suggesting evidence of the omission of small studies showing no increase in mortality or association with carbapenem exposure to carbapenem resistance or other kinds of statistical heterogeneity.

Discussion

A significant number of studies highlighting the emergence of carbapenem resistance among cancer patients have been published during the past decade, while only a few reports between 1995 and 2005 addressed the issue of CR in cancer patients.[41,42] In our review, the number of reports documenting carbapenem resistance increased considerably from 2005. High variability was shown according to geographic location, with highest rates documented in studies from south-eastern Europe, Israel and the Middle East.

Data from the Meropenem Yearly Susceptibility Test Information Collection (MYSTIC) programme between 1997 and 2000 showed that carbapenems had nearly 100% susceptibility among isolates from the neutropenic group.[43] Recent surveillance studies detailing the distribution of CR in patients with neutropenia, however, are not currently available, limiting the knowledge of resistance patterns in this patient population. Similarly, large studies analysing risk factors for the development of CR in this patient population are lacking. Although an association between disease type or severity (AML, salvage therapy, non-autologous HSCT and prolonged neutropenia) and carbapenem resistance has been postulated, we could not confirm these data in our review due to the paucity of studies analysing this correlation.[13,22] As previously documented, we observed a higher number of GNB BSIs compared with Gram-positive BSIs.[6]

Consistent with other studies in cancer patients, our review reports alarming rates of carbapenem resistance in *Pseudomonas* spp., even in areas with low rates of antimicrobial resistance such as northern Europe.[44,45] *Acinetobacter* spp. also showed high prevalence of antimicrobial resistance in neutropenic patients.[25–31] Less common were CR Enterobacteriaceae, documented mainly from countries with high CR-Kp prevalence.[11,13,15]

Only two studies in our review analysed molecular mechanisms of carbapenem resistance. The study of molecular patterns, however, can help to predict the type of resistances in a certain area or identify the reason for different distributions of resistance among pathogens. Increasing prevalences of KPC-Kp and metallo-β-lactamase (MBL)-producing *P. aeruginosa*, for example, were reported in various European and Mediterranean countries.[46] KPC genes were

Table 2. Distribution of CR isolates among the included studies

	CR isolates		CR *Pseudomonas* spp.		CR *Acinetobacter* spp.		CR Enterobacteriaceae	
Reference	BSI (%)	GNB (%)	*Pseudomonas* spp. (%)	CR isolates (%)	*Acinetobacter* spp. (%)	CR isolates (%)	Enterobacteriaceae (%)	CR isolates (%)
Alshukairi *et al.*[12]	NR	7/48 (15)	NR	NR	NR	NR	NR	NR
Andria *et al.*[13]	103/423 (24)	103/423 (24)	15/82 (18)	15/103 (15)	9/27 (33)	9/103 (9)	*Klebsiella* spp. 46/101 (46)	46/103 (45)
							E. coli 13/141 (9)	13/103 (13)
							others 4/30 (13)	4/103 (4)
Kara *et al.*[14]	44/272 (16)[a]	44/272 (16)	5/36 (14)	5/44 (11)	22/38 (58)	22/44 (50)	*Klebsiella* spp. 4/59 (7)	4/44 (9)
Trecarichi *et al.*[15]	72/263 (27)	72/353 (20)	47/66 (71)	47/72 (65)	—	—	*Klebsiella* spp. 15/43 (35)	15/72 (21)
							E. coli 3/187 (2)	3/72 (4)
							Enterobacter spp. 2/26 (8)	2/72 (3)
Kikuchi *et al.*[16]	NR	NR/NR (53)	NR	NR	NR	NR	NR	NR
Moghnieh *et al.*[17]	7/43 (16)	7/43 (16)	1/5 (20)	1/7 (14)	1/2 (50)	1/7 (14)	*Enterobacter* spp. 3/17 (17)	3/7 (43)
El-Mahallawy *et al.*[18]	NR	NR/NR (20)	NR	NR	NR	NR	NR	NR
Gedik *et al.*[19]	6/49 (12)	6/49 (12)	1/7 (14)	1/6 (17)	4/4 (100)	4/6 (67)	*Serratia marcescens* 1/2 (50)	1/6 (17)
Kwon *et al.*[20]	NR	5/119 (4)	4/5 (80)[b]	4/5 (80)	—	—	—	—
Kjellander *et al.* [21]	NR	6/372 (2)	5/42 (12)	5/6 (83)	—	—	*Enterobacter* spp. 1/43 (2)	1/6 (17)
Mudau *et al.*[22]	NR	NR	8/10 (80)	NR	NR	NR	NR	NR
Huang *et al.*[23]	NR	NR/NR (3)	NR	NR	NR	NR	NR	NR
Han *et al.*[24]	1/47 (2)	1/47 (2)	—	—	1/1 (100)	1/1 (100)	—	—
Chen *et al.*[25]	NR	11/516 (2)	4/47 (9)	4/11 (36)	7/54 (13)	7/11 (64)	—	—
Jin *et al.*[26]	3/25 (12)	3/25 (12)	3/3 (100)[c]	3/3 (100)	—	—	—	—
Jeddi *et al.*[27]	1/13 (8)	1/16 (6)	NR[d]	NR	NR	NR	NR	NR
Suárez *et al.*[28]	NR	NR	2/12 (17)	NR	NR	NR	NR	NR
Garnica *et al.*[29]	3/56 (5)	3/56 (5)	NR	NR	NR	NR	NR	NR
Mikulska *et al.*[30]	18/54 (33)	18/67 (27)	8/18 (44)	8/18 (44)	—	—	*Klebsiella* spp. 1/7 (14)	1/18 (6)
							Enterobacter spp. 1/7 (14)	1/18 (6)
Irfan *et al.*[31]	NR	42/442 (10)	8/86 (9)	8/42 (19)	34/58 (59)	34/42 (81)	—	—
Kim *et al.*[32]	NR	NR	NR	NR	13/18 (72)	NR	NR	NR
Baskaran *et al.*[33]	NR	4/44 (9)	1/4 (25)	1/4 (25)	—	—	*Enterobacter* spp. 1/5 (20)	1/4 (25)
Oliveira *et al.*[34]	5/34 (15)	5/59 (8)	4/13 (31)	4/5 (80)	1/6 (17)	1/5 (20)	—	—
Paul *et al.*[35]	NR	NR/NR (5)[e]	NR	NR	NR	NR	NR	NR
Solano *et al.*[36]	1/9 (11)	1/9 (11)	NR	NR	NR	NR	NR	NR
Wang *et al.*[37]	NR	19/327 (6)	19/327 (6)	19/19 (100)	NR	NR	—	—
Fanci *et al.*[38]	7/85 (8)	7/87 (8)	7/34 (21)	7/7 (100)	—	—	—	—
Gaytan-Martinez *et al.*[9]	1/21 (5)	1/24 (4)	—	—	—	—	*E. coli* 1/10 (10)	1/1 (100)
Krcméry *et al.*[40]	NR	NR	8/81 (10)	NR	NR	NR	NR	NR

NR, not reported.
[a]Polymicrobial BSIs were not considered.
[b]3/4 imipenem resistant, 0/4 meropenem-resistant.
[c]One strain became CR during therapy.
[d]High carbapenem resistance in *P. aeruginosa* reported (>50%, R. Jeddi, M. Achour, R. B. Amor, L. Aissaoui, W. Bouterâa, K. Kacem, R. B. Lakhal, H. B. Abid, Z. BelHadjAli, A. Turki and B. Meddeb, unpublished results).
[e]Increase from 5% to 15% after 15 days of hospitalization.

associated with TEM-, SHV- and CTX-M-15-producing strains among CR Enterobacteriaceae while MBL genes (IMP and VIM) were present in CR *Acinetobacter* spp. isolates.[32,47] In our study, CR *Klebsiella* spp. was limited to areas with high KPC-Kp rates, probably due to KPC gene dissemination by plasmid spread which is common during outbreaks in high-prevalence countries. Infections caused by CR in *Pseudomonas* spp., instead, were reported in sites with relatively low antibiotic resistance. This can be related to *Pseudomonas* efflux system-based resistance that can be altered by exposure to various antimicrobials (e.g. fluoroquinolones), resulting in accumulation of resistance to multiple classes of antibiotics.[48] We found that previous exposure to carbapenem was more frequently associated with carbapenem resistance rather than carbapenem susceptibility. While two studies reported the duration of exposure to carbapenems, none detailed antibiotic doses, limiting the evaluation of dose–response effects.

The mortality rates for CR GNB infections found in our studies are comparable to those of other reports.[49,50] We identified, however, a higher risk of mortality associated with CR BSIs in neutropenic patients compared with CS infections. These data are yet to

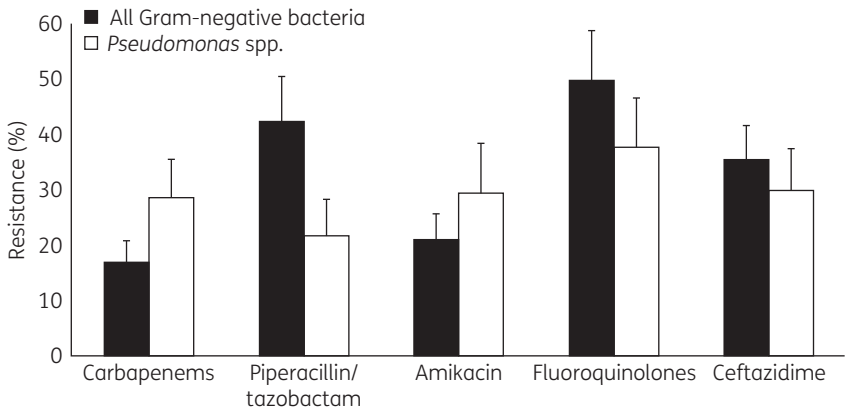

Figure 3. Percentages of resistance to carbapenems, piperacillin/tazobactam, amikacin, fluoroquinolones and ceftazidime among GNB and *Pseudomonas* spp. (expressed as percentage of all *Pseudomonas* isolates) from BSIs in neutropenic patients.

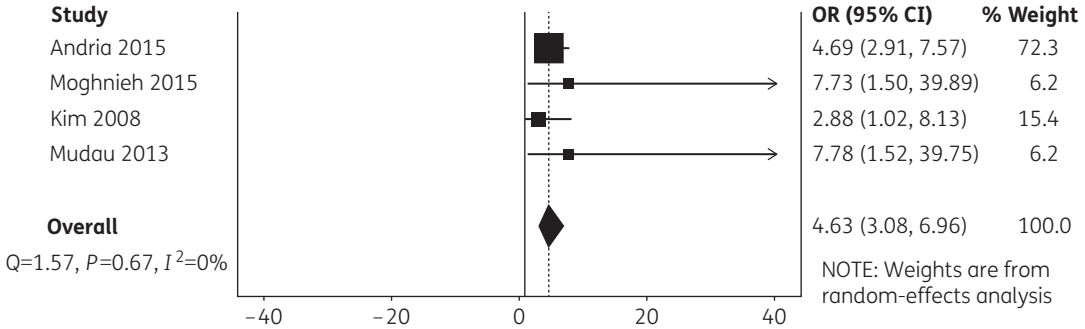

Figure 4. Forest plot of the association of carbapenem resistance with previous carbapenem exposure. Squares represent study-specific estimates (size of the square reflects the study-specific statistical weight, i.e. the inverse of the variance), horizontal lines represent 95% CI and diamonds represent summary estimates with corresponding 95% CI.

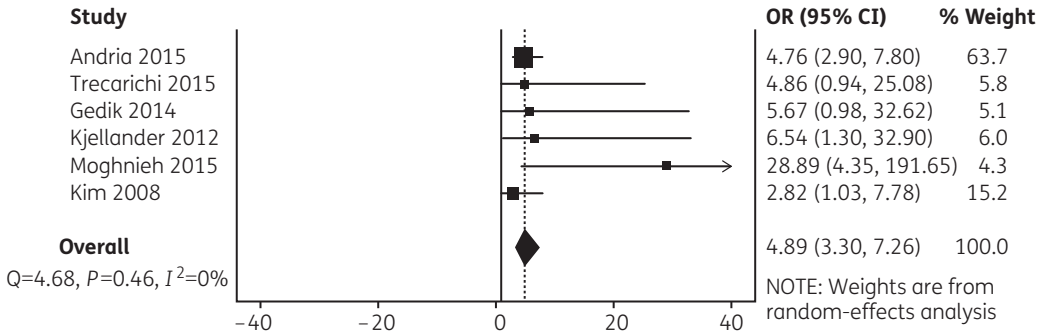

Figure 5. Forest plot of the association of carbapenem resistance with mortality for BSIs in neutropenic patients. Squares represent study-specific estimates (size of the square reflects the study-specific statistical weight), horizontal lines represent 95% CI and diamonds represent summary estimates with corresponding 95% CI.

be confirmed in large prospective studies and have often been attributed to inadequate therapy.[51]

We are aware of several limitations of our study. First, the determination of prevalence and the results of the meta-analyses were based on data mostly deriving from retrospective studies. The availability of patient-level data was therefore limited, although the largest study included in the meta-analysis adjusted data for confounders of mortality. Second, even if the geographic distribution of carbapenem resistance in our study was comparable to that reported for non-neutropenic populations, prevalence rates can vary widely among different centres and may not be representative of a country. Furthermore, centres with high rates of antibiotic resistance are more likely to report carbapenem resistance data compared with sites with lower resistance rates. This could have

Table 3. Factors associated with acquisition and outcome of CR BSIs

	Characteristic	
Reference	carbapenem resistance	mortality
Tofas *et al.*[11]	NR	multivariate analysis (14 day mortality): • unresolved neutropenia ($P = 0.006$) • septic shock ($P = 0.04$) • monotherapy ($P = 0.02$)
Andria *et al.*[13]	univariate analysis: • salvage therapy, non-autologous transplant ($P = 0.02$) • CR carrier status ($P < 0.001$) • *Klebsiella* spp. infections, polymicrobic BSI ($P = 0.07$) • prolonged hospitalization, low functional capacity ($P < 0.001$) • carbapenem treatment < 30 days ($P < 0.001$) • inappropriate treatment ($P < 0.001$)	multivariate analysis (14 day mortality): • carbapenem resistance ($P < 0.001$) • high comorbidity, low functional capacity, salvage therapy ($P = 0.007$) • septic shock ($P < 0.001$) • polymicrobic BSI ($P = 0.02$)
Trecarichi *et al.* [15]	NR	21 day mortality higher in CR-Kp compared with CS *K. pneumoniae* ($P = 0.04$)
Moghnieh *et al.* [17]	univariate analysis: • piperacillin/tazobactam and carbapenem-based regimens > 4 days ($P = 0.05$)	univariate analysis: • carbapenem resistance correlated with death, sepsis and intubation ($P < 0.001$)
Gedik *et al.* [19]	NR	30 day mortality higher in CR strains
Kjellander *et al.* [21]	NR	30 day mortality higher in CR strains
Mudau *et al.*[22]	univariate analysis: • metronidazole ($P = 0.005$) and imipenem use ($P = 0.001$) multivariate analysis: • AML ($P = 0.01$), amikacin, metronidazole use ($P = 0.02$)	NR
Kim *et al.* [32]	multivariate analysis • neutropenia ($P = 0.039$) • carbapenem use > 7 days ($P = 0.030$) (for MBL strains, cephalosporin use > 7 days)	higher in CR strains

NR, not reported.

introduced a significant publication bias in our study. The methodology for determination of carbapenem resistance also varied across studies and CR rates may have been underestimated by the use of automated identification systems. Third, a selection bias could have been introduced in the meta-analysis investigating the correlation of carbapenem use with carbapenem resistance by the use of control patients who had the antimicrobial-susceptible form of the organism.[52] Overall, these limitations highlight the need for well-designed studies documenting the impact of CR in neutropenic patients in order to provide useful information for the management of BSI in this patient population.

Conclusions

To our knowledge, this is the first systematic review and meta-analysis to explore the characteristics of carbapenem resistance in neutropenic patients with BSIs.

The emergence of new resistance profiles affects patient outcomes and impacts antimicrobial stewardship. Carbapenem resistance, in particular, appears problematic for clinicians seeking an adequate empirical therapy to treat cancer patients with severe infections. Although carbapenems are frequently used as first-line therapy in hospital settings with high rates of cephalosporin resistance, their use could often be replaced by carbapenem-sparing regimens that are still effective for treating ESBL-producing organisms.[53,54] In settings with significant presence of CR-producing organisms, combinations of 'old' antimicrobials such as colistin, tigecycline and aminoglycosides (with or without a carbapenem) are currently employed.[55,56] Their use in empirical therapy, however, can be associated with significant toxicity and further selection of resistances, and needs to be supported by accurate laboratory detection of CR strains.[57] In HSCT patients with febrile neutropenia at high risk for CR-Kp infections (e.g. colonized with CR-Kp or during outbreaks) empirical combination of at least two active agents against

CR-Kp has been recommended.[58] The impact of this approach on patient outcomes, however, still needs to be demonstrated.

Given the likelihood that carbapenem use promotes CRE, antibiotic stewards need clear guidance about when alternatives to carbapenems can be used. New compounds with demonstrated efficacy against KPC-Kp, such as ceftazidime/avibactam, and CR (but not MBL-producing) *P. aeruginosa*, such as ceftolozane/tazobactam, are now available.[58] Their efficacy in febrile neutropenia, however, has not been validated.

The knowledge of patterns of resistance and specific factors associated with CR BSIs remains essential for their management among neutropenic patients. In this patient population, carbapenem-sparing options still need to be defined in order to limit the selection pressure for carbapenem resistance in GNB. Large prospective studies investigating prevalence, risk factors and outcome of CR infections in neutropenic patients are urgently needed.

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Transparency declarations

None to declare.

Supplementary data

Appendixes S1–S6 are available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/).

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