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Systematic review

Risk factors for carbapenem-resistant Gram-negative bacterial infections: a systematic review

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ABSTRACT

Background: Rapid and widespread increases in carbapenem resistance (CR) necessitate identification of risk factors to guide appropriate interventions.
Objectives: We aimed to identify risk factors for CR Gram-negative infection through a systematic literature review.
Data sources: We searched MEDLINE (via OvidSP and PubMed) and Embase (via OvidSP) databases and the Cochrane Central Register of Controlled Trials.
Study eligibility criteria: Prospective or retrospective cohort and case–control studies reporting quantitative data on risk factors associated with infections due to CR Gram-negative pathogens in hospitalized patients were eligible.
Participants: Studies included hospitalized patients with CR infection caused by Gram-negative bacterial pathogens (Enterobacterales and non-fermenters).
Methods: Searches were conducted in January 2018/December 2019 to identify studies published since 2007. Risk factor data were extracted and grouped by factor. The primary metric was proportion of studies reporting a significant association with CR infection for each factor.
Results: In total, 92 studies were identified. Risk factors most frequently reported as significantly associated with CR infection (>10 studies) were previous antibiotic use (91.1%; 72/79 studies); previous carbapenem use (82.6%; 57/69); previous colonization (72.7%; 8/11); mechanical ventilation (66.7%; 36/54); previous intensive care unit stay (64.4%; 38/59); dialysis (61.1%; 11/18); catheter (58.0%; 40/69); length of stay in hospital (54.5%; 30/55); comorbidities (52.7%; 39/74); APACHE II (51.7%; 15/29); and intubation (51.4%; 18/35). Risk factors were mostly consistent across different species and sites of infection.
Conclusions: Several variables, particularly previous antibiotic use, are strong risk factors for CR infection. Interventions to mitigate against CR infection should target these factors.
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Background

In recent years, increases in bacterial resistance to carbapenems have been observed globally, frequently mediated by the acquisition

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of carbapenemase enzymes against which few antibiotics remain active. Given the problematic nature of treatment for carbapenem-resistant (CR) Gram-negative organisms, including a high co-occurrence of resistance to multiple classes of antibiotics (multi-drug resistance; MDR), efforts are required to counter increases in CR. As a foundation for these efforts, it is important to establish the important risk factors for CR infections. Identified factors can then form the basis for targeted interventions to reduce the ongoing dissemination and spread of CR Gram-negative organisms.

Previous systematic reviews have examined risk factors for CR infections, but have been limited by a focus only on specific bacterial pathogens, e.g. *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* [1,2], or have examined risk factors more broadly for MDR bacteria [3,4]. Our objective for this systematic review is to synthesize the available literature reporting risk factors for CR Gram-negative infections among hospitalized patients, to enable identification of targets for interventions to reduce the incidence and impact of this global problem.

Methods

Eligibility criteria

This systematic review explores potential risk factors predisposing to clinical infections caused by CR Gram-negative organisms in hospitalized patients. Prospective or retrospective observational cohort and case–control studies were eligible for inclusion if they reported quantitative data on the risk factors associated with clinical infections due to CR Gram-negative pathogens in hospitalized patients. Cohort studies are defined as any studies that compared two groups of patients that differed in terms of exposure followed over time. Both cohort and case–control studies were required to include patients with carbapenem-susceptible (CS) infections as a control group. Carbapenem susceptibility was as defined by the study authors. Studies reporting on colonization only were excluded. Studies were required to have been published in English as full texts from 2007 onwards. This cut-off date was selected because the first major reports highlighting the increase in CR in Gram-negative pathogens in Europe emerged in 2008 [5,6]. Detailed eligibility criteria are shown elsewhere (please see supplementary material).

Literature search

A protocol for this systematic review was developed *a priori* and registered on the PROSPERO database (CRD42018087699). The search strategy comprised two concepts: 'carbapenem resistance' and specific infections. Searches were conducted in MEDLINE, EMBASE, CENTRAL and PubMed. The full MEDLINE search strategy is shown elsewhere (please see supplementary material). We also identified prior relevant systematic reviews and checked their included studies list to ensure that we had identified and assessed relevant studies. The searches were conducted in January 2018 and updated in December 2019, when database searches were re-run in full, and deduplicated within-set and against the previous results.

Study selection

Study selection was conducted by two independent reviewers with conflicts adjudicated by a third reviewer.

Data extraction

A single reviewer performed data extraction and risk of bias assessment; a second reviewer checked every data point; a third reviewer adjudicated any disagreements. A full list of the data elements extracted from each study are reported elsewhere (please see supplementary material). The risk of bias tools used were Newcastle Ottawa Scale [7] for case–control studies and the Centre for Reviews and Dissemination tool for cohort studies [8]. Had any randomized controlled trials been identified, the protocol specified that the Cochrane risk of bias tool would have been used to assess bias in these studies [9]. The risk of bias assessment is included elsewhere (please see supplementary material).

Data synthesis

Risk factors were divided into seven groups for analysis: antibiotic use; clinical severity assessment scale scores; patient demographics (age, sex and ethnicity); surgery; non-surgical invasive procedures (including indwelling devices); exposure to the hospital environment; and 'Other' (risk factors not captured elsewhere, including colonization; a full list is provided elsewhere (please see supplementary material). Many studies examined a large number of different risk factors and so are included across multiple risk factor groups.

The significance of the association between the risk factors assessed in each study and the occurrence of CR infection was investigated by examining the statistical data reported in the study. Studies reporting a significant association between a certain risk factor and CR infection were noted as such, and p values and odds ratios (OR) for the associations were recorded. These data were taken from the univariate analysis reported by each study. If not reported by the study, and if data permitted, ORs were calculated by the reviewers. Where adjusted multivariate analyses were included in a study, these are reported separately.

Given the large volume of data reported in the systematic review, the data presented here have synthesized broad associations between risk factors and CR infection based on the proportions of studies reporting significance for each risk factor. Data are reported overall, by Gram-negative pathogen and by infection site. We also explored whether there were any differences in reporting or risk factors according to the local endemicity of CR (established by cross-referencing the country with the degree of endemicity highlighted in Bonomo et al. [10]) or the size of the study (number of patients).

Owing to the significant heterogeneity of the studies in terms of study design, patient populations and included pathogens, statistical pooling was not deemed appropriate, and so comparative statistical analysis or meta-analysis of the results was not possible.

Results

Across the two searches (January 2018 and December 2019), 12 702 unique records were assessed for relevance. Following full text review, 116 studies were eligible. However, some of these studies compared patients with CR infection with uninfected patients only or a control group comprising both uninfected patients and patients with CS infection. For the reasons noted in the Methods section, all authors agreed to focus the review on studies including patients with CS infections as the control group ($n = 92$; references in supplementary material). Details of the selection process can be found in the PRISMA flow diagram in Fig. 1.

Table 1 shows a summary of the studies included in the analysis. Cohort studies were generally of moderate to high risk of bias, primarily due to the poor reporting, while case–control studies were considered to have a low to moderate risk of bias (please see supplementary material). *K. pneumoniae* was the most frequently investigated pathogen followed by mixed pathogens, *Acinetobacter*

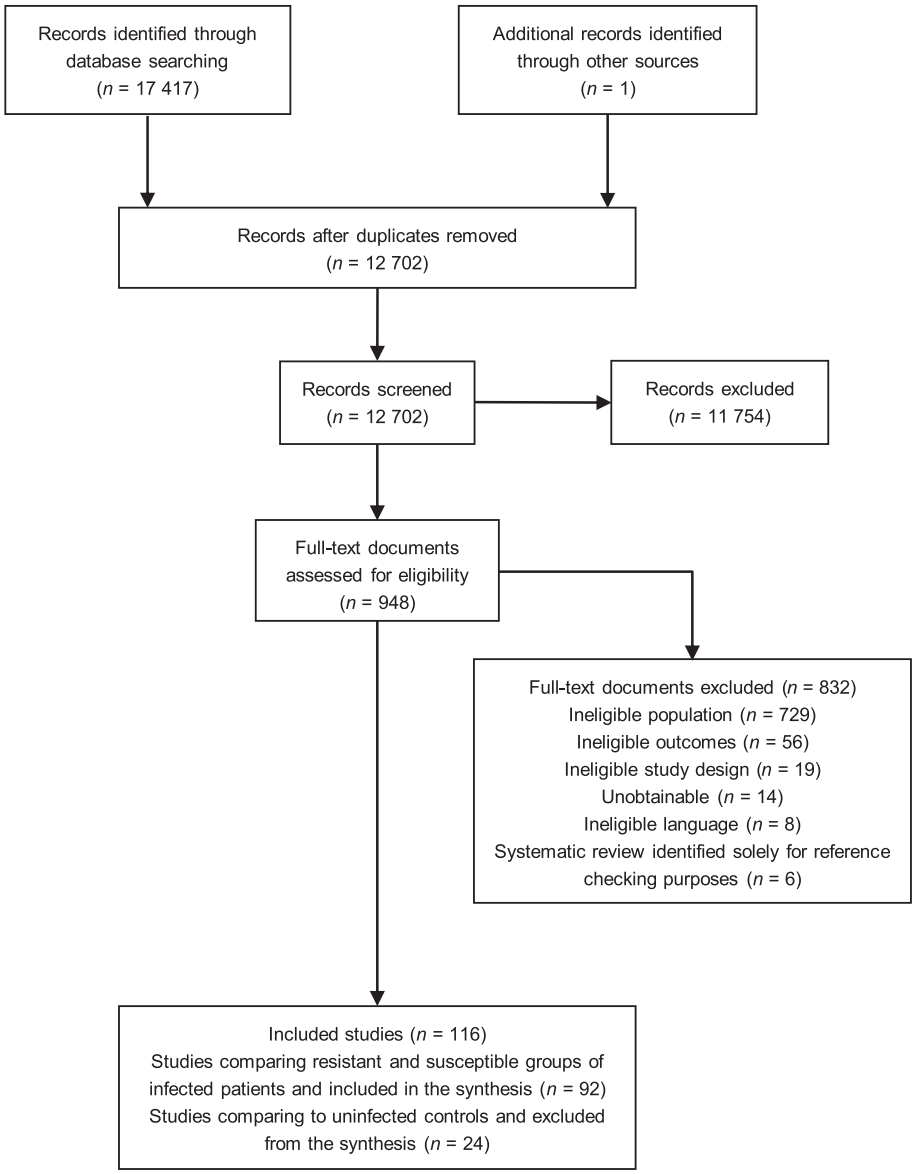

Fig. 1. PRISMA flow diagram.

baumannii and *P. aeruginosa*. Of 40 studies that reported where the infection was acquired, 35 studies reported nosocomial acquisition and five acquisition in a community healthcare setting. Two studies (Jamulitrat, 2009; Hoxha, 2016; see Supplementary Appendix 6 for details) only reported outcome data without explicit definition of risk factors and so were excluded from the analyses.

Risk factors

The association between risk factors and CR infection by univariate analysis is shown in Table 2. The factors reported as significant in the highest proportion of studies are shown in Fig. 2. The risk factor most frequently found to be significantly associated with CR infection was antibiotic use, in 91.1% of studies (72/79) examining this factor. Of specific antibiotic classes examined, carbapenem use was found to be associated with CR infection in 82.6% of studies (57/69). For all other classes except colistin (for which 57.1% of studies (4/7) found a significant association), the percentage of studies finding a significant association was <50% (range: 22.0% (9/41) to 38.9% (21/54)).

Antibiotic use was also found to be associated with CR infection in studies that included a multivariate analysis (Table 3), with 51.9% of studies (41/79) finding a significant association between antibiotic use and CR infection. This percentage was considerably higher than for other risk factor groups, where the range of percentages of studies finding a significant association with CR infection was 2.6% (2/76) to 30.8% (24/78) (Table 4). The multivariate analyses also showed that use of carbapenems was found to have an association with CR infection in the highest proportion of studies (42.2% of studies; 30/71), compared with other antibiotic classes (range: 3.8% (1/26) to 20.0% (11/55)). This pattern was consistent across each of the Gram-negative pathogens included in the systematic review, with no obvious differences between species.

Beyond antibiotic use, the individual risk factors most frequently reported as significantly associated with CR infection on univariate analysis were Pitt Score (100% of studies; 8/8); previous colonization with relevant bacteria, including CR isolates

Table 1
Summary of details of the 92 studies included in the analysis

	Studies ($N = 92$)
Study type	
Case–control	78
Cohort	14
Country of study	
China	18
United States of America	16
Turkey	10
Taiwan	9
Greece	8
Brazil	7
Israel	5
India	3
Thailand	3
Colombia	2
France	2
Lithuania	2
Serbia	2
Algeria	1
Georgia	1
Italy	1
Malaysia	1
Republic of Korea	1
Sample size	
<50 patients	7
50–200 patients	62
200–500 patients	14
>500 patients	5
Unknown[a]	4
Number of sites	
Single site	79
Multicentre	13
Pathogen focus	
Acinetobacter baumannii	19
Acinetobacter nosocomialis	1
Escherichia coli	1
Klebsiella pneumoniae	35
Pseudomonas aeruginosa	17
Mixed populations	19

[a] Studies reported number of isolates rather than patients.

(72.7%; 8/11); non-specific device use (75.0%; 6/8); mechanical ventilation (66.7%; 36/54); previous intensive care unit (ICU) stay (64.4%; 38/59); dialysis (61.1%; 11/18); catheter placement of any type (58.0%; 40/69); length of stay in hospital (54.5%; 30/55); presence of a comorbidity (52.7%; 39/74); Acute Physiology and Chronic Health Evaluation II Score (51.7%; 15/29); and intubation (gastric/nasogastric/tracheal tube) (51.4%; 18/35).

A high proportion of studies reported significant associations between the heterogeneous group of 'Other risk factors' and CR (72.0%; 59/82).

In the analysis of risk factors according to CR endemicity, no significant differences in risk factor associations could be observed between groups, although study numbers were small for many comparisons. A similar result was observed in the analysis by study size.

Several potential risk factors were found not to be significantly associated with CR infection. Prior surgery was found to be associated with CR infection in 23.4% of studies (11/47), with no notable differences between surgery at a prior visit or at the current visit. In most studies investigating demographics, these were found not to be associated with CR infection. For gender, a very mixed picture emerged; significant association with CR infection or CS infection was reported in approximately equivalent proportions of studies.

Subgroup analyses of risk factors

The risk factors most significantly associated with CR infections by univariate analysis according to infecting pathogen and infection site are shown elsewhere (please see supplementary material). Overall, the risk factors most frequently associated with CR infections were consistent across the different pathogens and infection sites. Antibiotic use was reported as a significant risk factor in >85% of studies for all pathogens. Of specific antibiotic classes, prior use of carbapenems was most frequently reported as significant (>75% of studies for all pathogens). For other classes, generally less than 50% of studies reported use as a significant risk factor. Across the different infection sites, antibiotic use was reported as a significant risk factor in ≥90% of studies for all infection sites, except complicated intra-abdominal infections (87.5% of studies) and studies where infection site was not reported (80.0% of studies). Carbapenem use was reported as significant across all infection sites (>80% for all infection sites, except studies where infection site was not reported; 60.0% of studies).

Discussion

In this systematic review, several risk factors were frequently associated with CR infections caused by Gram-negative bacteria in hospitalized patients, most notably exposure to antibiotics, and particularly carbapenems. Other risk factors included use of invasive devices and procedures, such as mechanical ventilation and catheterization, and exposure to the hospital environment, particularly the ICU. These results echo those of previous systematic reviews examining related, though not identical, questions [2,3].

While the association between antibiotic use and CR infection is intuitive, it highlights the need to implement and maintain high standards of antimicrobial stewardship to reduce over-reliance on certain classes of antibiotics, particularly carbapenems, to reduce selection pressure for CR. Indeed, the selective pressure of antibiotics, including carbapenem, has been linked not only to CR [11–13], but also MDR [14] by complex and often heterogeneous mechanisms [13,14]. Antimicrobial stewardship initiatives may vary depending on the local CR prevalence. In endemic CR regions, general use of colistin as empirical therapy may be appropriate, although colistin is known to be less effective than modern antibiotics [15]. Conversely, where CR prevalence is low or moderate, carbapenem-sparing strategies may be implemented. In extended spectrum β-lactamase infections, use of conventional (i.e. piperacillin/tazobactam) or novel β-lactam/β-lactamase inhibitor combinations may be appropriate, with fosfomycin, aminoglycosides and temocillin reasonable options in patients with complicated urinary tract infection [16]. Overall, further research is required to identify optimal treatment regimens [17]. Furthermore, despite our findings that there were no significant differences in CR risk factor associations between groups based on endemicity, this was likely mostly due to the small number of studies included in each endemicity category. As such, it is possible that a significant relationship between antibiotic exposure, particularly carbapenem exposure, and CR might be observed in high endemicity regions.

The co-occurrence of and complex interplay between resistance mechanisms for independent antibiotic classes must also be considered [18]. For example, some agents, notably fluoroquinolones, are known to enhance the CR mutation rate in *P. aeruginosa* [19].

Beyond antibiotic use, the risk factors most frequently associated with CR infection were related to invasive devices or procedures and exposure to the hospital environment, particularly the ICU, as expected [2,20,21]. Indeed, many of the risk factors associated with exposure to the hospital environment (e.g. ICU stay and mechanical ventilation) are interlinked, and so caution should be taken during interpretation.

The risk factors most frequently associated with CR infection were fairly consistent across the different pathogens studied. The

Table 2
Proportion of studies demonstrating an association between chosen risk factors and carbapenem resistance infections

Risk factor group/ individual factor	Studies examining risk factor grouping, *n* (%)	Significant association with CR infection, *n (%)*								
		Overall	Range of odds ratios for CR-significant studies	Endemicity			Study size			
				High	Medium	Low	*N* > 500	200 < *N* < 500	50 < *N* < 200	*N* < 50
Antibiotic use	79 (85.9)	72/79 (91.1)	1.18–78.17	35/37 (94.6)	25/27 (92.6)	11/14 (78.6)	3/4 (75.0)	14/14 (100)	48/50 (96.0)	4/7 (57.1)
Unspecified agent	53 (57.6)	36/53 (67.9)	1.4–78.17	19/30 (63.3)	13/16 (81.3)	3/6 (50.0)	3/3 (100)	6/6 (100)	19/38 (50.0)	3/4 (75.0)
Unspecified broad-spectrum agent	3 (3.3)	2/3 (66.7)	1.4–53.21	1/1 (100)	1/1 (100)	0/1 (0.0)	—	1/2 (50.0)	—	—
Specific antibiotic classes										
Aminoglycoside	41 (44.6)	9/41 (22.0)	1.18–25.92	5/17 (29.4)	3/14 (21.4)	1/10 (10.0)	0/1 (0.0)	5/9 (55.6)	4/26 (15.4)	0/3 (0.0)
β-lactam/β-lactamase inhibitor	35 (38.0)	13/35 (37.1)	2.22–5.69	2/13 (15.4)	8/17 (47.1)	3/5 (60.0)	0/2 (0.0)	7/10 (70.0)	6/22 (27.3)	0/1 (0.0)
β-lactam/penicillin	26 (28.3)	10/26 (38.5)	2.17–8.57	6/13 (46.2)	0/3 (0.0)	4/10 (40.0)	1/1 (100)	5/5 (100)	4/19 (21.1)	1/2 (50.0)
Carbapenem	69 (75.0)	57/69 (82.6)	1.2–75.05	26/31 (83.9)	22/25 (88.0)	8/12 (66.7)	1/2 (50.0)	13/14 (92.9)	39/44 (88.6)	2/6 (33.3)
Cephalosporin	55 (59.8)	20/55 (36.4)	2.23–32.67	8/20 (40.0)	5/22 (22.7)	6/12 (50.0)	1/2 (50.0)	8/13 (61.5)	9/28 (32.1)	1/6 (16.7)
Colistin	7 (7.6)	4/7 (57.1)	4.17–12.1	3/5 (60.0)	1/2 (50.0)	—	—	1/1 (100)	3/6 (50.0)	—
Fluoroquinolone	54 (58.7)	21/54 (38.9)	1.87–20.62	9/21 (42.9)	8/22 (36.4)	4/11 (36.4)	1/2 (50.0)	8/13 (61.5)	11/35 (31.4)	1/4 (25.0)
Other	38 (41.3)	21/38 (55.2)	1.977–19.86	7/16 (43.8)	11/15 (73.3)	3/7 (42.9)	1/1 (100)	6/9 (66.7)	14/25 (56.0)	0/3 (0.0)
Clinical severity assessment scores	45 (48.9)	26/45 (59.1)	1.04–14.00	7/19 (36.8)	11/16 (68.8)	8/10 (80.0)	2/4 (50.0)	9/11 (81.8)	13/25 (52.0)	2/5 (40.0)
APACHE II Score	29 (31.5)	15/29 (51.7)	1.04–8.33	4/12 (33.3)	8/13 (61.5)	3/4 (75.0)	0/1 (0.0)	8/9 (88.9)	5/14 (35.7)	2/5 (40.0)
Charlson Comorbidity Index	13 (14.1)	4/13 (30.8)	1.44	2/7 (28.6)	1/3 (33.3)	1/3 (33.3)	1/3 (33.3)	0/3 (0.0)	3/7 (42.9)	—
McCabe Score	5 (5.4)	1/5 (20.0)	2.31	1/1 (100)	0/4 (0.0)	—	—	0/1 (0.0)	1/4 (25.0)	—
Pitt Score	8 (8.7)	8/8 (100)	2.96–14.00	1/1 (100)	3/3 (100)	4/4 (100)	1/1 (100)	2/2 (100)	5/5 (100)	—
SOFA Score	6 (6.5)	2/6 (33.3)	4.08	1/3 (33.3)	0/2 (0.0)	1/1 (100)	1/1 (100)	1/5 (20.0)	—	—
SAPS II Score	2 (2.2)	0/2 (0.0)	—	0/1 (0.0)	0/1 (0.0)	—	—	—	0/2 (0.0)	—
Other	5 (5.4)	2/5 (40.0)	4.39–14.00	0/2 (0.0)	2/3 (66.7)	—	—	1/2 (50.0)	1/3 (33.3)	—
Demographics	76 (82.6)	15/76 (19.7)	1.03–7.83	8/35 (22.9)	5/25 (20.0)	1/15 (6.7)	1/3 (33.3)	2/14 (14.3)	11/50 (22.0)	1/7 (14.3)
Age	72 (78.3)	9/72 (12.5)	1.03	3/32 (9.4)	5/24 (20.8)	1/15 (6.7)	0/3 (0.0)	2/14 (14.3)	7/46 (15.2)	0/7 (0.0)
Ethnicity	5 (5.4)	2/5 (40.0)	1.25–7.83	2/5 (40.0)	—	—	1/1 (100)	—	1/3 (33.3)	—
Sex	73 (79.3)	6/73 (8.2)	1.94–5.63	5/33 (15.2)	0/25 (0.0)	0/14 (0.0)	1/4 (25.0)	1/14 (7.1)	3/47 (6.4)	1/7 (14.3)
Hospital-related factors	86 (93.5)	60/86 (69.8)	1.01–50.4	35/43 (81.4)	14/28 (50.0)	11/15 (73.3)	3/4 (75.0)	11/14 (78.6)	42/59 (71.2)	2/6 (33.3)
Hospital-acquired infection	10 (10.9)	4/10 (40.0)	4.49–4.65	0/2 (0.0)	2/6 (33.3)	2/2 (100)	1/2 (50.0)	2/4 (50.0)	1/4 (25.0)	—
ICU stay	59 (64.1)	38/59 (64.4)	1.58–33.01	19/30 (63.3)	13/18 (72.2)	6/11 (54.5)	1/1 (100)	9/11 (81.8)	25/42 (59.5)	1/3 (33.3)
Length of stay	55 (59.8)	30/55 (54.5)	1.01–17.6	18/29 (62.1)	6/16 (37.5)	6/10 (60.0)	3/3 (100)	6/11 (54.5)	20/37 (54.1)	1/1 (100)
Prior hospitalization	41 (44.6)	15/41 (36.6)	2.5–13.15	8/20 (40.0)	5/15 (33.3)	2/6 (33.3)	0/3 (0.0)	4/9 (44.4)	11/27 (40.7)	0/3 (0.0)
Specific admission reason/location (excl. ICU)	8 (8.7)	2/8 (25.0)	2.01–2.72	0/2 (0.0)	1/4 (25.0)	1/2 (50.0)	0/1 (0.0)	1/2 (50.0)	1/4 (25.0)	0/1 (0.0)
Other	11 (12.0)	5/11 (45.5)	1.1–50.4	4/8 (50.0)	1/2 (50.0)	0/1 (0.0)	—	2/2 (100)	3/9 (33.3)	—
Invasive procedures/devices (excl. surgery)	78 (84.8)	59/78 (75.6)	1.03–129.15	28/36 (77.8)	19/27 (70.4)	11/15 (73.3)	3/4 (75.0)	11/12 (91.7)	37/53 (69.8)	5/6 (83.3)
Catheter placement	69 (75.0)	40/69 (58.0)	1.74–70.81	17/30 (56.7)	14/24 (58.3)	8/14 (57.1)	2/3 (66.7)	9/11 (81.8)	22/46 (47.8)	4/6 (66.7)
Diagnostic procedures	6 (6.5)	2/6 (33.3)	1.73–3.09	—	2/5 (40.0)	0/1 (0.0)	0/1 (0.0)	1/1 (100)	1/4 (25.0)	—
Dialysis	18 (19.6)	11/18 (61.1)	2.64–9.00	4/8 (50.0)	6/8 (75.0)	1/1 (100)	1/1 (100)	4/6 (66.7)	4/8 (50.0)	0/1 (0.0)
Drainage	12 (13.0)	3/12 (25.0)	2.14–2.93	0/4 (0.0)	2/6 (33.3)	1/2 (50.0)	—	3/3 (100)	0/6 (0.0)	0/2 (0.0)
Intubation (gastric/nasogastric/tracheal)	35 (38.0)	18/35 (51.4)	1.49–19.8	7/13 (53.8)	8/12 (66.7)	2/9 (22.2)	1/1 (100)	5/6 (83.3)	9/21 (42.9)	1/4 (25.0)
Mechanical ventilation	54 (58.7)	36/54 (66.7)	1.03–25.88	12/22 (54.5)	14/19 (73.7)	9/12 (75.0)	1/2 (50.0)	11/12 (91.7)	20/34 (58.8)	2/4 (50.0)
Non-specific devices	8 (8.7)	6/8 (75.0)	2.5–14.11	4/5 (80.0)	1/1 (100)	1/2 (50.0)	—	1/1 (100)	4/6 (66.7)	1/1 (100)
Nutrition support therapy	22 (23.9)	10/22 (45.5)	2.17–5.7	5/11 (45.5)	1/6 (16.7)	4/5 (80.0)	1/2 (50.0)	3/4 (75.0)	6/15 (40.0)	0/1 (0.0)
Other	7 (7.6)	5/7 (71.4)	2.76–129.15	3/3 (100)	1/2 (50.0)	1/2 (50.0)	—	2/2 (100)	3/5 (60.0)	—
Transfusion	5 (5.4)	2/5 (40.0)	2.43–9.11	1/4 (25.0)	1/1 (100)	—	—	—	2/4 (50.0)	0/1 (0.0)
Surgery	47 (51.1)	11/47 (23.4)	1.94–20.0	5/19 (26.3)	5/20 (25.0)	1/7 (14.3)	0/1 (0.0)	2/8 (25.0)	9/33 (27.3)	0/5 (0.0)
Prior admission	20 (21.7)	5/20 (25.0)	1.94–20.0	1/8 (12.5)	4/11 (36.4)	0/1 (0.0)	0/1 (0.0)	2/4 (50.0)	3/13 (23.1)	0/2 (0.0)
Current admission	31 (33.7)	6/31 (19.4)	2.53–5.9	4/14 (28.6)	1/10 (10.0)	1/6 (16.7)	—	0/4 (0.0)	6/24 (25.0)	0/3 (0.0)
Other risk factors	82 (89.1)	59/82 (72.0)	1.05–50.4	32/40 (80.0)	18/28 (64.3)	9/14 (64.3)	3/4 (75.0)	12/14 (85.7)	41/54 (75.9)	0/6 (0.0)
Previous colonization	11 (12.0)	8/11 (72.7)	4.44–47.65	6/7 (85.7)	0/2 (0.0)	2/2 (100)	2/2 (100)	1/1 (100)	5/8 (62.5)	—
Comorbidity	74 (80.4)	39/74 (52.7)	1.22–33.75	17/35 (48.6)	15/27 (55.6)	7/12 (58.3)	3/4 (75.0)	11/13 (84.6)	24/49 (49.0)	0/5 (0.0)

Many studies examined multiple individual risk factors; therefore, counts and proportions are based on studies finding a significant association with CR infection on any individual risk factor tested; study size columns total less than 100% as several studies reported numbers of isolates or infections instead of patient numbers.
CR, carbapenem resistant; ICU, intensive care unit.

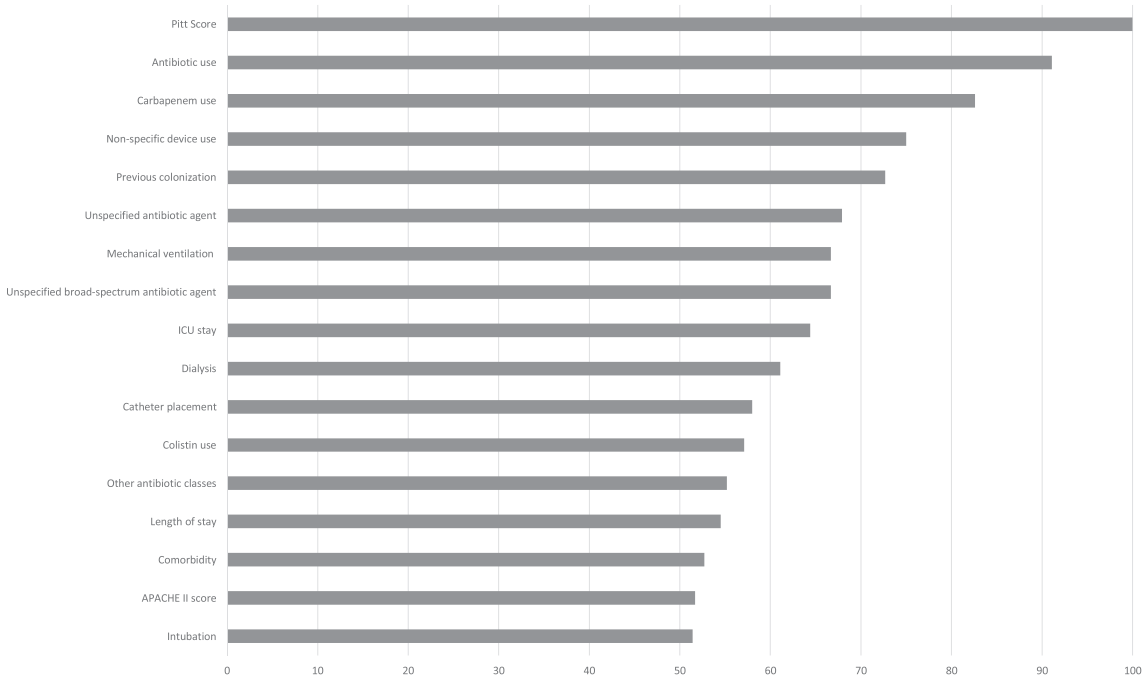

Fig. 2. Individual risk factors most frequently reported to have a significant association with CR infection by univariate analysis. APACHE, Acute Physiology and Chronic Health Evaluation; CR, carbapenem resistant.

high proportion of studies reporting antibiotic use and carbapenem use (both 100%) as a significant risk factor for CR infection with mixed pathogens may have been due to the inclusion of *Stenotrophomonas maltophilia,* a species constitutively resistant to carbapenems [22], in addition to other Gram-negative pathogens. The higher proportion of studies reporting a significant association with clinical severity assessment scores for bloodstream infections may have been driven by the higher proportion of these studies examining the Pitt Score, which was significant in all studies in which it was assessed.

A key limitation of the systematic review was the variation in the number of studies included for each of the risk factors. In addition, the studies themselves were generally limited in terms of reporting, with cohort studies found to be of lower quality than case–control studies, by risk of bias assessment. We have not conducted an analysis by study type and therefore cannot determine if study design has been a confounding factor. Furthermore, some of the studies did not report risk factors according to the number of patients but instead by the number of isolates or infections [23–25]. Therefore, caution needs to be taken when interpreting risk factors associated with these studies. Ideally, a meta-analysis of the results would have been conducted; however, the heterogeneity of included studies precluded this, as even for those studies that included multivariate analysis, concerns existed regarding the comparability of these data. These concerns are: (a) huge variation across the studies in variables considered in the multivariate analysis; (b) some studies only considered variables that were significant at the univariate level while others considered all; and (c) details of how the variables were considered in the analyses were inconsistent and often poorly reported. Multivariate analysis of carbapenem use would have been further limited by the fact that cohort studies could not include this variable if no patient received carbapenems in the CS infection group, or if the univariate OR for this variable was very large (infinite or very large ORs would lead to unstable regression models). Beyond the studies reporting multivariate analyses, no other studies featured alternative methods of adjustment.

In addition, several limitations of the review should also be considered. Owing to the large volume of literature available, we chose to balance precision and sensitivity for our search, focusing on studies with 'carbapenem resistance' explicitly stated in the database record. Therefore, studies that only explicitly referred to CR infections in the full text may not have been identified. In addition, CR in Gram-negative bacterial infections is a broad concept. While it has clinical relevance in referring to patients that would not benefit from receiving empirical treatment with carbapenems, there are substantial differences among species from a risk factor identification perspective. This issue has been relevant for study selection and analyses.

The results of this systematic review should be interpreted with caution, as it is difficult to separate risk factors that are specific for CR infection from factors that increase the risk of nosocomial infections in general. For example, central venous catheter use and admission to ICU, both identified as risk factors in our systematic review, are also risk factors for nosocomial infections [26]. Importantly, while this systematic review is a useful starting point for identification of risk factors, it is limited by the heterogeneity and relatively small scale of the studies included. In addition, our choice of studies employing patients with CS infections as the control group may have influenced the size of the effect estimates in each study [27,28]. Indeed, the choice of control group for an analysis of risk factors is controversial—the estimation of risk for antibiotic resistance may vary depending on whether uninfected patients or patients with susceptible infections are used as the control group [27,28]. However, the use of an uninfected control group would not have allowed us to distinguish between risk factors for the organism in general and the resistant phenotype of the organism [29], and our research question was to determine risk factors for infection with a CR pathogen among patients with that pathogen in general [30].

Table 3
Summary of studies reporting significant association with CR infections on multivariate analysis, by risk factor: studies examining antibiotic use; also includes an analysis by infecting pathogen

Risk factor	Studies showing significant association with CR on multivariate analysis, *n (%)* (range of odds ratios for significant studies)						
	Overall	*Acinetobacter baumannii*	*Acinetobacter nosocomialis*	*Pseudomonas aeruginosa*	*Escherichia coli*	*Klebsiella pneumoniae*	Mixed pathogens
Antibiotic use	41/79 (51.9) (1.01–360.72)	8/18 (44.4) (2.57–80.65)	1/1 (100) (6.36–N/A)	8/15 (53.3) (1.99–360.72)	1/1 (100) (29.17)	18/29 (62.1) (1.01–40.32)	4/14 (28.6) (1.07–11.37)
Unspecified agent	10/53 (18.9) (1.08–38.4)	2/11 (18.2) (5.05–20.06)	—	1/8 (12.5) (5.0)	—	6/22 (27.3) (1.08–38.4)	0/11 (0)
Unspecified broad-spectrum agent	2/3 (66.7) (11.25–N/A)	1/2 (50.0) (N/A)	—	—	—	—	—
Specific antibiotic classes							
Aminoglycoside	2/41 (4.9) (11.8–34.8)	1/10 (10.0) (11.8–N/A)	0/1 (0.0)	0/8 (0.0)	0/1 (0.0)	1/15 (6.7) (34.8–N/A)	0/6 (0.0)
β-Lactam/β-lactamase inhibitor	3/35 (8.6) (4.77–5.6)	1/8 (12.5) (5.6–N/A)	0/1 (0.0)	1/8 (12.5) (5.0–N/A)	—	1/15 (6.7) (4.77–N/A)	0/3 (0.0)
β-lactam/penicillin	1/26 (3.8) (3.58–N/A)	0/7 (0.0)	0/1 (0.0)	0/3 (0.0)	0/1 (0.0)	0/7 (0.0)	1/7 (14.3) (3.58–N/A)
Carbapenem	30/71 (42.2) (1.01–360.72)	6/14 (42.9) (2.57–54.8)	1/1 (100) (6.36)	7/15 (46.7) (1.99–360.72)	1/1 (100) (29.17)	11/26 (42.3) (1.01–25.12)	3/12 (25.0) (3.6–11.37)
Cephalosporin	11/55 (20.0) (1.22–28.1)	3/14 (21.4) (2.6–8.14)	0/1 (0.0)	1/9 (11.1) (3.33–N/A)	0/1 (0)	6/23 (26.1) (1.22–28.05)	1/7 (14.3) (3.49–N/A)
Colistin	1/7 (14.3) (1.07–N/A)	0/1 (0.0)	—	0/2 (0.0)	—	0/3 (0)	1/1 (100) (1.07–N/A)
Fluoroquinolone	7/54 (13.0) (1.76–80.65)	1/12 (8.3) (80.65–N/A)	0/1 (0.0)	1/12 (8.3) (5.41)	0/1 (0.0)	5/21 (23.8) (1.76–28.9)	0/7 (0.0)
Other	6/38 (15.8) (3.3–40.32)	1/8 (12.5) (32.9–N/A)	—	0/6 (0.0)	0/1 (0.0)	4/17 (23.5) (3.3–40.32)	1/6 (16.7) (7.75–N/A)

Table 4
Summary of studies reporting significant association with CR infections on multivariate analysis, by risk factor: studies examining other risk factors

Risk factor	Studies showing significant association with CR on multivariate analysis, *n* (%)	Risk factor subgroups showing significant association on multivariate analysis	Range of odds ratios for significant studies
Clinical severity assessment scores	7/45 (15.6)	APACHE II Score; Pitt Score; McCabe Score	1.1–7.68
Demographics	2/76 (2.6)	Percentage of patients aged >60 years; mean age	1.06–2.16
Hospital-related factors	20/86 (23.3)	Hospital-acquired infection; ICU stay; length of stay; prior hospitalization	1.02–22.2
Invasive procedures/devices (excl. surgery)	24/78 (30.8)	Catheter use; diagnostic procedures; dialysis; drainage; intubation (gastric/nasogastric/tracheal); mechanical ventilation; nutrition support therapy; transfusion	1.07–37.55
Surgery	2/47 (4.3)	Surgery at current admission; surgery at prior admission	15.99–35.98
Other risk factors	24/82 (29.3)	Cancer; colonization with Gram-negative pathogens (with or without CR); colonization with vancomycin-resistant Enterococci; comorbidities; transplant	1.6–98.58

APACHE, Acute Physiology and Chronic Health Evaluation; CR, carbapenem resistant; ICU, intensive care unit; N/A, not applicable.

Our work requires further validation in epidemiological studies assessing the probability of CR in association with each risk factor, individually or in combination, in larger populations of patients.

Notwithstanding the limitations outlined above, this systematic review represents a valuable step in providing a more complete understanding of risk factors for CR infection. This is increasingly important, as targeted interventions to minimise CR risk can reduce the negative outcomes associated with resistant infections. These outcomes affect individual patients in terms of mortality and morbidity, and the healthcare system as a whole in terms of increased resource use and costs of treatment [31,32].

In conclusion, this timely and as yet unique systematic review summarises available data on risk factors for the acquisition of CR Gram-negative infections among hospitalized patients with specific risk factors. Above all, previous antibiotic use, in particular carbapenem use, was the risk factor most frequently identified. Additional risk factors included use of invasive devices and exposure to the hospital environment. These factors were found to be significant both overall, and across the different pathogens and sites of infection included in the study. These data will provide useful information to identify appropriate effective interventions to reduce CR risk in hospitalized patients.

Transparency declaration

J.R.B., K.M., M.G., P.V., R.Mc C. and Z.R.P.B. have no conflict of interest to declare. SL and CL are currently employees of Shionogi Europe. D.M. is a former employee of Shionogi Europe.

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Author contributions

C.L., D.M., J.R.B., M.G., P.V., S.L. and Z.RP.B. provided input into the study design. R.Mc C. and K.W. developed the research question and systematic review protocol, and conducted study selection and synthesis. KW also conducted data extraction and risk of bias checking. All authors were involved in the drafting of the manuscript, and provided in-depth review and final approval of the version to be submitted.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2020.10.016.

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