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Bacteraemia due to multidrug-resistant Gram-negative bacilli in cancer patients: risk factors, antibiotic therapy and outcomes

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Objectives: To assess the risk factors, antibiotic therapy and outcomes of multidrug-resistant Gram-negative bacilli (MDRGNB) bacteraemia in hospitalized patients with cancer.

Methods: Episodes of MDRGNB bacteraemia were compared with a susceptible control group in a 4 year prospective study.

Results: Of 747 bacteraemias, 372 (49.7%) were caused by a Gram-negative bacilli (GNB). Fifty-one of these (13.7%) were caused by a multidrug-resistant (MDR) strain. Previous antibiotics [odds ratio (OR) 3.57; 95% confidence interval (CI) 1.63–7.80] and urinary catheter (OR 2.41; 95% CI 1.01–5.74) were identified as independent risk factors for MDRGNB acquisition. The most frequent mechanism of resistance was extended-spectrum β-lactamase (ESBL) production (45%), mainly by *Escherichia coli*, followed by Amp-C cephalosporinase hyperproduction (24%). Patients with MDRGNB bacteraemia more frequently received inadequate initial antibiotic therapy (69% versus 9%; $P<0.001$) and time to adequate therapy was longer in this group (41% versus 4%; $P<0.001$). Patients in the resistant group more frequently required intensive care unit (ICU) admission (14% versus 5%; $P=0.023$), had greater need for mechanical ventilation (14% versus 3%; $P=0.005$) and had a higher overall case-fatality rate (41% versus 21%; $P=0.003$). Risk factors for mortality were solid tumour (OR 5.04; 95% CI 2.49–10.19), current corticosteroid use (OR 4.38; 95% CI 2.39–8.05), ICU admission (OR 11.40; 95% CI 3.19–40.74) and MDRGNB bacteraemia (OR 3.52; 95% CI 1.36–9.09).

Conclusions: MDRGNB bacteraemia was common among cancer patients, especially in those exposed to antibiotics and urinary catheter. The most frequent mechanism of resistance was ESBL production. Patients with MDRGNB more frequently received inadequate empirical antibiotic therapy and presented poorer outcomes with a higher overall case-fatality rate (within 30 days).

Keywords: bloodstream infection, immunosuppression, neutropenia, antibiotic resistance

Introduction

Bacteraemia is a common complication in immunosuppressed patients with cancer receiving chemotherapy and in stem cell transplant recipients, and is associated with high morbidity and mortality rates. The epidemiology of bacteraemia in cancer patients occurring during neutropenia has changed in the past decades, with the re-emergence of Gram-negative bacilli (GNB) as the leading causative agents. The development of multidrug resistance among these organisms has become a major health problem worldwide. This problem is of particular concern among immunosuppressed patients with cancer, who are at especially high risk for severe sepsis and poor outcome. Treatment of infections due to multidrug-resistant GNB (MDRGNB) is

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a clinical challenge. Nevertheless, information regarding risk factors for MDRGNB bacteraemia in immunosuppressed patients with cancer and its outcome is scarce and dispersed. The aim of the present prospective study is to assess the frequency, risk factors, antibiotic therapy and outcomes of MDRGNB bacteraemia in cancer patients.

Methods

Setting, patients and study design

We conducted a prospective observational study in a 200-bed university referral cancer centre for adults in Barcelona, Spain. From January 2006 to December 2009 all hospitalized cancer patients and haematopoietic stem cell transplant (HSCT) recipients with at least one episode of bacteraemia were included in the study. Information on baseline characteristics, clinical features, empirical antibiotic therapy and outcomes was carefully recorded in a specific database.

For the purposes of this study, patients were divided into two groups: patients with bacteraemia due to a MDRGNB and those with bacteraemia due to a susceptible GNB (henceforth 'MDRGNB' and 'non-MDRGNB'). The two groups were compared in order to identify risk factors for multidrug-resistant (MDR) infection. We also compared patients who died with those who survived in order to determine the independent factors influencing mortality. All bacteraemia episodes at our hospital are reported and followed up by an infectious disease physician; some have been described previously.[1] Changes in antimicrobial treatment and general management were advised when necessary. During the study period, no antibacterial prophylaxis to prevent bacterial infections was administered to patients with neutropenia. The study was approved by the ethics committee of our institution.

Definitions

Patients were considered to have a MDR infection in the following situations: (i) extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae; (ii) AmpC cephalosporinase hyperproducing Enterobacteriaceae; (iii) β-lactamase OXA-type-producing Enterobacteriaceae; (iv) microorganisms with intrinsic resistance mechanisms such as *Stenotrophomonas maltophilia*; and (v) MDR strains including *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. MDR strains were defined as those resistant to three or more classes of antibiotics: carbapenems (imipenem and meropenem); penicillins (piperacillin, ticarcillin and piperacillin/tazobactam); cephalosporins (ceftazidime and cefepime); monobactams; aminoglycosides; and fluorquinolones.[2] In cases of

Table 1. Baseline and demographic characteristics of all episodes of GNB bacteraemia in cancer patients

Characteristic	MDRGNB, $N=51$, n (%)	Non-MDRGNB, $N=312$, n (%)	P
Male sex	29 (57)	198 (63.5)	0.43
Age in years, median (range)	62 (23–89)	62 (14–89)	0.52
Underlying disease			
solid tumour	23 (45)	158 (51)	0.54
haematological malignancy	28 (55)	154 (49)	
HSCT	2 (4)	26 (8)	0.39
Graft-versus-host disease	0	9 (3)	0.62
Co-morbidities	27 (53)	114 (36.5)	0.030
diabetes mellitus	10 (20)	50 (16)	0.54
chronic obstructive pulmonary disease	4 (8)	29 (9)	1.00
chronic heart disease	9 (18)	33 (11)	0.15
chronic renal failure	2 (4)	8 (3)	0.63
chronic liver disease	4 (8)	16 (5)	0.50
Previous anti-neoplastic chemotherapy (within 1 month)	37 (72.5)	213 (68)	0.62
Neutropenia (<500 neutrophils/μL)	15 (29)	130 (42)	0.12
Previous radiotherapy (within 1 month)	3 (6)	31 (10)	0.44
Current corticosteroid therapy	17 (33)	132 (42)	0.28
Previous antibiotic therapy (within 1 month)	39 (76)	139 (45)	<0.001
Urinary catheter	13 (26)	32 (10)	0.004
Intravascular catheter	30 (59)	161 (52)	0.36
Parenteral nutrition	4 (8)	3 (1)	0.009
Previous surgery (within 1 month)	1 (2)	14 (4.5)	0.70
Previous ICU admission (within 3 months)	8 (16)	10 (3)	0.001
invasive mechanical ventilation (within 7 days)	3 (6)	0	0.003
Previous hospital admission (within 3 months)	32 (63)	170 (54.5)	0.29
Healthcare-related acquisition	49 (96)	282 (90)	0.28
Previous blood transfusion (within 5 days)	14 (28)	48 (15)	0.043
Previous episode of bacteraemia	8 (16)	13 (4)	0.004

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polymicrobial bacteraemia caused by a MDRGNB and a non-MDRGNB isolate, the episode was defined as a case.

Neutropenia was defined as an absolute neutrophil count <500/mm^3. Bacteraemia was considered to be nosocomially acquired, healthcare related or community acquired, applying the criteria described previously.[3] Current corticosteroid therapy was recorded when a patient was receiving corticosteroids at the time of the episode of bacteraemia or in the previous month. Prior antibiotic therapy was defined as the receipt of any systemic antibiotic >48 h in the preceding 30 days. Bacteraemia was considered to be from an endogenous source in neutropenic patients in whom no other bacteraemia sites were identified. Shock was defined as a systolic pressure <90 mmHg that was unresponsive to fluid treatment or required vasoactive drug therapy.[4] Empirical antibiotic therapy was considered inadequate if the treatment regimen did not include at least one antibiotic active *in vitro* against the infecting microorganism. In patients with ESBL-*Escherichia coli* (ESBL-EC), bacteraemia treatment with an oxyimino β-lactam (combined or not with an aminoglycoside) was considered inadequate, regardless of the MIC. Early case-fatality rate was defined as death within 7 days of the bacteraemia episode. Overall case-fatality rate was defined as death by any cause within the first 30 days of the onset of bacteraemia.

Microbiological studies

Identification of microorganisms and susceptibility testing were performed using commercial panels CN1S from the MicroScan automated system (Siemens Healthcare Diagnostics Ltd). CLSI criteria were used to define susceptibility or resistance to antimicrobial agents.[5] ESBL production was screened and confirmed in all isolates with a profile suggestive of resistance by performing a double-disc synergy test in accordance with CLSI guidelines.[6] Carbapenemase production was investigated in carbapenem-resistant strains with non-intrinsic resistance to carbapenems, performing a modified Hodge method as described in the CLSI guidelines, and a double-disc synergy test with EDTA discs for metallo-β-lactamase screening.[6,7] ESBLs were characterized by a multiplex PCR. The presence of bla_{TEM}, bla_{SHV}, $bla_{CTX\text{-}M}$ and bla_{OXA} in each organism was studied by PCR, as described previously.[8] Molecular characterization of ESBL-EC was performed by macrorestriction analysis of genomic DNA restricted with XbaI (New England BioLabs). DNA fragments were separated by PFGE in a CHEF-DR III system (Bio-Rad). Restriction patterns were analysed by applying previously established criteria.[9]

Statistical analysis

Continuous variables were compared by the Mann–Whitney *U*-test and the *t*-test. Qualitative variables were compared by the χ^2 test; odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. Multivariate logistic regression analysis of factors potentially associated with MDRGNB acquisition and mortality included all statistically significant variables in univariate analysis, sex and age, and all clinically important variables, whether they were statistically significant or not.[10] Measures of goodness-of-fit were obtained to assess the performance of the models. The analysis was performed with the stepwise logistic regression model of the SPSS software package (SPSS).

Results

During the study period 747 episodes of bacteraemia were recorded. Out of 372 (49.7%) episodes caused by GNB, 51 were due to a MDR strain (13.7%). Ten episodes of Gram-negative bacteraemia were excluded from the analysis because they occurred within less than 4 weeks after a first episode of GNB bacteraemia, and they were considered to be recurrent episodes (the causative microorganism was the same in both episodes). The outcomes of these 10 recurrent episodes were already analysed in the first episode. Thus 363 episodes were finally eligible for the analyses. In the control group, 27 patients presented more than one episode (312 episodes in 276 patients), whereas in the MDRGNB group there was one episode of bacteraemia per patient. The distribution of cases during the four-year study period did not suggest the occurrence of outbreaks.

The baseline and demographic characteristics of the patients according to the study group (MDRGNB and non-MDRGNB) are shown in Table 1. Variables such as age, sex, underlying disease and neutropenia were similar between groups. The presence of other co-morbidities, antibiotics in the previous month, urinary catheter, parenteral nutrition, previous intensive care unit (ICU) admission, invasive mechanical ventilation, previous blood transfusion and previous episode of bacteraemia were more frequently found among the MDRGNB group. After applying a logistic regression model (Table 2) the only independent risk factors for MDR acquisition were prior antibiotic exposure (OR 3.57; 95% CI 1.63–7.80) and urinary catheter (OR 2.41; 95% CI 1.01–5.74). The goodness-of-fit test of Hosmer and Lemeshow showed good agreement between observed and predicted values of the model (P=0.21).

The 38 MDRGNB Enterobacteriaceae and their phenotypic β-lactam resistance profiles were, in order of frequency: *E. coli* (n=25) [ESBL production (n=20), AmpC cephalosporinase hyperproduction (n=2) and β-lactamase OXA-1 production (n=3)]; *Enterobacter cloacae* (n=5) [AmpC cephalosporinase

Table 2. Risk factors for MDRGNB acquisition by multivariate analysis

Characteristic	MDRGNB, N=51, n (%)	Non-MDRGNB, N=312, n (%)	P	Adjusted OR (95% CI)	P
Male sex	29 (57)	198 (63.5)	0.43	1.81 (0.93–3.67)	0.078
Age in years, median (range)	62 (23–89)	62 (14–89)	0.52	0.98 (0.99–1.03)	1.00
Co-morbidities	27 (53)	114 (36.5)	0.030	1.60 (0.77–3.33)	0.20
Previous antibiotic therapy	39 (78)	139 (45)	<0.001	3.57 (1.63–7.80)	0.001
Previous ICU admission	8 (16)	10 (3)	0.001	2.11 (0.59–7.54)	0.24
Urinary catheter	13 (26)	32 (10)	0.004	2.41 (1.01–5.74)	0.047
Parenteral nutrition	4 (8)	3 (1)	0.009	2.67 (0.37–18.89)	0.32
Previous blood transfusion	14 (28)	48 (16)	0.043	1.55 (0.69–3.46)	0.27
Previous episode of bacteraemia	8 (16)	13 (4)	0.004	2.28 (0.77–6.77)	0.13

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hyperproduction ($n=4$) and ESBL production ($n=1$)]; *Enterobacter aerogenes* ($n=3$) (AmpC cephalosporinase hyperproduction); *Klebsiella* spp. ($n=3$) [*Klebsiella pneumoniae* ESBL production ($n=2$) and *Klebsiella oxytoca* chromosomal β-lactamase hyperproduction ($n=1$)]; *Aeromonas hydrophila* ($n=1$) (AmpC cephalosporinase hyperproduction); and *Morganella morganii* ($n=1$) (AmpC cephalosporinase hyperproduction). Rates of resistance to non-β-lactam antibiotics among ESBL-Enterobacteriaceae were as follows: gentamicin 13% (3/23), tobramycin 13% (3/23), ciprofloxacin 91.3% (21/23) and co-trimoxazole 56.5% (13/23). All strains were susceptible to amikacin and carbapenems. The ESBLs were characterized in 19 available strains: 14 from the CTX-M family, 3 from the SHV family and 2 from the TEM family (TEM-52). All the ESBL-Enterobacteriaceae strains were shown to be different by PFGE. The 13 remaining MDRGNB non-Enterobacteriaceae were, in order of frequency: *P. aeruginosa* ($n=7$), *A. baumannii* ($n=3$) and *S. maltophilia* ($n=3$). Five *P. aeruginosa* and all *A. baumannii*

Table 3. Clinical features, antibiotic treatment and outcome of patients with MDRGNB bacteraemia compared with the susceptible control group

Characteristic	MDRGNB, $N=51$, *n* (%)	Non-MDRGNB, $N=312$, *n* (%)	*P*
Clinical features			
axillary temperature ≥38°C	40 (78)	251 (80)	0.85
source of bacteraemia			
endogenous bacteraemia	13 (25.5)	110 (35)	0.20
urinary tract	12 (23.5)	66 (21)	0.71
cholangitis	12 (23.5)	52 (17)	0.23
gastrointestinal tract	3 (6)	36 (11.5)	0.32
pneumonia	2 (4)	13 (4)	1.00
spontaneous bacterial peritonitis	0	3 (1)	1.00
other[a]	3 (6)	9 (3)	0.23
unknown origin	6 (12)	23 (7)	0.27
polymicrobial bacteraemia	6 (12)	38 (12)	1.00
concomitant infection[b]	5 (10)	11 (3.5)	0.056
shock at presentation	5 (10)	39 (12.5)	0.81
Empirical antibiotic treatment	48 (94)	306 (98)	0.11
combination therapy	16 (33)	153 (50)	0.043
β-lactam+aminoglycoside	15 (94)	136 (89)	1.00
β-lactam+glycopeptide	1 (6)	8 (5)	0.60
β-lactam+quinolone	0	6 (4)	1.00
other combinations	0	3 (2)	1.00
monotherapy	32 (67)	153 (50)	0.043
β-lactam+β-lactam inhibitor	21 (66)	108 (71)	0.67
carbapenem	8 (25)	30 (20)	0.47
oxyimino β-lactam	6 (19)	13 (8.5)	0.10
quinolone	0	13 (8.5)	0.12
aminoglycoside	0	3 (2)	1.00
glycopeptide	0	3 (2)	1.00
other	1 (3)	2 (1)	0.43
Inadequate initial empirical antibiotic therapy[c]	35 (69)	29 (9)	<0.001
Time to adequate antibiotic therapy >48 h	21 (41)	13 (4)	<0.001
ICU admission	7 (14)	14 (4)	0.023
Invasive mechanical ventilation	7 (14)	10 (3)	0.005
Early case-fatality rate (7 days)	9 (18)	33 (11)	0.15
Overall case-fatality rate (30 days)	20 (39)	62 (20)	0.003

[a]Catheter-related bacteraemia, 8; skin and soft tissue infection (SSTI), 2; and disseminated infection, 2.
[b]In the MDRGNB group: *Campylobacter jejuni* colitis, 2; invasive pulmonary aspergillosis (IPA), 1; *Clostridium difficile* (CD) colitis, 1; and pneumonia, 1. In the non-MDRGNB group: IPA, 2; CD colitis, 1; neutropenic enterocolitis, 1; disseminated herpes zoster virus infection, 1; SSTI, 1; cytomegalovirus (CMV) colitis, 1; CMV antigenaemia, 1; CMV pneumonitis, 1; catheter-related infection, 1; and aspiration pneumonia, 1.
[c]Nine cases who did not receive any empirical antibiotic therapy were considered to have received inadequate therapy.

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Table 4. Risk factors for overall mortality by univariate and multivariate analysis

Risk factor	Survived, $N=267$, n (%)	Died, $N=82$, n (%)	P	Adjusted OR (95% CI)	P
Male sex	164 (61)	55 (67)	0.43	1.06 (0.56–2.00)	0.84
Age in years, median (range)	61 (14–89)	66 (23–89)	0.043	1.02 (0.99–1.05)	0.062
Solid tumour	115 (43)	56 (68)	<0.001	5.04 (2.49–10.19)	<0.001
Graft-versus-host disease	4 (1.5)	5 (6)	0.036	5.40 (0.82–35.39)	0.079
Other co-morbidities	94 (35)	39 (48)	0.051	0.92 (0.48–1.74)	0.80
Polymicrobial bacteraemia	29 (11)	15 (18)	0.087	—	—
Concomitant infection	10 (4)	7 (8.5)	0.085	—	—
Current corticosteroid therapy	85 (32)	55 (67)	<0.001	4.38 (2.39–8.05)	<0.001
Statin use	30 (11)	6 (7)	0.40		
Inadequate empirical antibiotic therapy	39 (15)	20 (24)	0.044	1.57 (0.50–4.90)	0.43
Time to adequate antibiotic therapy >48 h	16 (6)	14 (17)	0.003	2.36 (0.62–8.93)	0.20
Shock at presentation	23 (9)	20 (24)	<0.001	1.57 (0.68–3.61)	0.28
ICU admission	7 (3)	14 (17)	<0.001	11.40 (3.19–40.74)	<0.001
invasive mechanical ventilation	3 (1)	14 (17)	<0.001		
MDRGNB	29 (11)	20 (24)	0.003	3.52 (1.36–9.09)	0.009

strains were resistant to carbapenems and all other β-lactams. None was a carbapenemase producer. All *P. aeruginosa* and *A. baumannii* strains were resistant to ciprofloxacin and susceptible to amikacin and colistin. *S. maltophilia* strains were only susceptible to co-trimoxazole. In the control group, the GNB isolated were *E. coli* in 159 cases, *P. aeruginosa* in 57 cases, *K. pneumoniae* in 53 cases, *E. cloacae* in 18 cases, *Proteus mirabilis* in 9 cases, *Salmonella enteritidis* in 7 cases, *K. oxytoca* in 5 cases, *E. aerogenes* in 3 cases, *Citrobacter* spp. in 3 cases, *A. hydrophila* in 3 cases, *Serratia marcescens* in 3 cases, *M. morganii* in 2 cases, *Shewanella putrefaciens* in 2 cases, *A. baumannii* in 1 case and *Escherichia fergusoni* in 1 case (38 episodes were polymicrobial).

Clinical features, antibiotic treatment and patient outcomes are detailed in Table 3. When comparing episodes caused by a MDRGNB with those caused by a non-MDRGNB, no differences regarding clinical features at presentation were found. The most frequent focus of bacteraemia was an endogenous source (34% of the episodes), followed by urinary tract (21.5%) and cholangitis (17.6%). The great majority of patients received empirical antibiotic therapy (97.5%), with no differences between groups regarding the antibiotic type received. Patients with MDRGNB bacteraemia more frequently received inadequate initial empirical antibiotic therapy compared with the susceptible control group, and time to adequate antibiotic therapy was longer in this group. Among the patients who received inadequate initial empirical antibiotic therapy, adequate therapy lasted more than 48 h in 21/35 patients (60%) in the MDRGNB group and 13/29 patients (45%) in the non-MDRGNB group. The mean time to adequate therapy was 2.13 days (±1.6 SD) in the MDRGNB group, versus 0.33 days (±0.98 SD) in the non-MDRGNB group, $P<0.001$. Bacteraemia due to a MDR strain was also associated with a poorer outcome, with higher ICU admission, greater need of invasive mechanical ventilation and a higher overall case-fatality rate.

Table 4 summarizes the results of the univariate and multivariate analysis of factors potentially associated with the overall case-fatality rate. After adjustment, independent risk factors for mortality were solid tumour as the underlying disease (OR 5.04; 95% CI 2.49–10.19), current corticosteroid therapy (OR 4.38; 95% CI 2.39–8.05), ICU admission (OR 11.40; 95% CI 3.19–40.74) and MDRGNB bacteraemia (OR 3.52; 95% CI 1.36–9.09). The goodness-of-fit test of Hosmer and Lemeshow showed good agreement between observed and predicted values of the model ($P=0.22$).

Discussion

In this prospective study we found that 13.7% of episodes of bacteraemia in cancer patients were caused by a MDRGNB. This finding is in line with recent studies, which report an increase in antibiotic resistance among GNB in immunocompetent and immunocompromised hosts, including patients with malignancies and HSCT recipients.[11–17]

The identification of risk factors associated with the development of specific types of infection may be an important step forward in predicting infection and in guiding implementation of strategies to decrease its incidence and negative impact. In our study, urinary catheter and previous antibiotic therapy were found to be independent risk factors for MDRGNB bacteraemia. Previous antibiotic therapy has been recognized as a major risk factor for bacterial resistance development,[1,11,12,14,15,18–20] and urinary catheter has also been identified as a risk factor, especially for ESBL production, in non-immunosuppressed patients.[11,20] In our study of cancer patients, this finding may be explained by the high prevalence of ESBL-EC isolates, and also by the notably high number of bloodstream infections originating in the urinary tract (21.5%).

The majority of the MDR isolates were *E. coli*, mostly ESBL producers, followed by *Enterobacter* spp. and *P. aeruginosa*. The most frequent non-MDRGNB were *E. coli*, followed by *P. aeruginosa* and *K. pneumoniae*. This finding is representative of an immunosuppressed population with cancer and frequently associated neutropenia, although it may vary according to the local epidemiology.[12,15,21] We found extensive clonal diversity

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among all ESBL-EC isolates, with a clear predominance (74%) of ESBL type CTX-M. These findings have also been described previously by other studies performed in the same geographic area.[1,22]

A relationship between infection with resistant bacteria and poor outcome has been reported in several settings.[17,23–26] In line with these findings, we observed that patients with MDRGNB received inadequate empirical antibiotic therapy more frequently than patients with non-MDRGNB, and time to adequate therapy was also longer in this group. Moreover, patients with MDRGNB bacteraemia had poor outcomes, with frequent ICU admission, need for mechanical ventilation and a high overall case-fatality rate. Although inadequate empirical antibiotic therapy has been related with mortality in GNB bacteraemia,[20,23–27] this association was not found in the present study. A short delay in receiving appropriate antimicrobial therapy does not necessarily lead to an adverse outcome.

Clinical outcomes of patients with bacteraemia may also depend on several factors such as underlying condition, severity of illness, primary site of infection and causative organism.[23] In our study, independent factors influencing mortality were solid tumour, current corticosteroid therapy, ICU admission and MDRGNB bacteraemia. Mortality occurred mainly in debilitated patients with uncontrolled solid tumours who were receiving palliative chemotherapy and corticosteroids in an attempt to mitigate the symptoms caused by the underlying disease.[28] Patients who required ICU admission for severe sepsis or further complications were also more likely to have a poorer outcome.

Treatment options for MDRGNB infections are often limited. Carbapenems are the drugs of choice for infections caused by ESBL-producing microorganisms, but their use may not be appropriate in infections caused by *P. aeruginosa*, *A. baumannii* or *S. maltophilia*, where resistance to carbapenems is increasing.[17] There are very few new antimicrobial agents against MDRGNB. The only new agent with significant *in vitro* activity is tigecycline, a glycylcycline derivative of the tetracycline minocycline, but clinical experience is limited and in fact resistance has already been reported. This drug is not active against *P. aeruginosa* or some strains of MDR *A. baumannii*. Moreover, since it is generally bacteriostatic, its use in cancer patients with neutropenia may not be recommended.

Choosing the initial empirical antibiotic therapy in patients with severe sepsis is often a clinical challenge, especially when a MDR microorganism is suspected. Surveillance data of the geographical area, the institution and the ward may be helpful in order to choose an optimal antibiotic regimen in each case, and antibiotic combinations are usually needed.[29] Cancer patients who present risk factors for MDRGNB infection, such as previous antibiotics and/or urinary catheter, might benefit from an empirical antibiotic therapy comprising a combination of a broad-spectrum β-lactam (e.g. a carbapenem) plus an aminoglycoside or a fluoroquinolone. The lack of new antibiotic options against Gram-negative pathogens underscores the need for optimization of current therapies and prevention of the spread of these organisms.

Despite a number of strengths, our prospective study of a large cohort of bacteraemias has some limitations that should be acknowledged. First, it was performed in a single institution, which may not reflect the epidemiology of different centres and/or different geographical areas. Second, we analysed a heterogeneous group of MDRGNB that may have different epidemiological and clinical characteristics and behaviours.

In conclusion, we found that bacteraemia caused by MDRGNB is common among cancer patients, especially in those exposed to antibiotic pressure and those carrying a urinary catheter. The most frequent mechanism of resistance was ESBL production (especially by *E. coli*), followed by AMP-c production. Patients with MDRGNB bacteraemia more frequently received inadequate initial antibiotic therapy and had a poorer outcome, with a greater need for ICU admission and a higher overall case-fatality rate. We were unable to establish whether increased mortality in patients with MDRGNB bacteraemia was directly associated with a delay in the appropriate antibiotic. In the absence of new antimicrobial agents against resistant GNB, judicious use of antibiotics and control measures to prevent the development and spread of GNB resistance are needed.

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Transparency declarations

None to declare.

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