Journal of Global Antimicrobial Resistance 25 (2021) 187–192

Contents lists available at ScienceDirect

Journal of Global Antimicrobial Resistance

journal homepage: www.elsevier.com/locate/jgar

Long-term outcome and risk factors for late mortality in Gram-negative bacteraemia: a retrospective cohort study

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ARTICLE INFO

Article history:
Received 18 January 2021
Revised 23 February 2021
Accepted 11 March 2021
Available online 2 April 2021

Editor: Professor E. Giamarellos-Bourboulis

Keywords:
Bacteraemia
Gram-negative bacteria
Mortality
Escherichia coli
Klebsiella
Pseudomonas aeruginosa

ABSTRACT

Objectives: The long-term outcomes of patients following Gram-negative bacteraemia (GNB) are poorly understood. Here we describe a cohort of patients with GNB over a 2-year period and determine factors associated with late mortality (death between Days 31 and 365 after detection of bacteraemia).

Methods: This was a single-centre, retrospective, observational cohort study of 789 patients with confirmed *Escherichia coli, Klebsiella* spp. or *Pseudomonas aeruginosa* bacteraemia with a follow-up of 1 year. Multivariable survival analysis was used to determine risk factors for late mortality in patients who survived the initial 30-day period of infection.

Results: Overall, 1-year all-cause mortality was 36.2%, with 18.1% of patients dying within 30 days and 18.1% of patients suffering late mortality. An adverse antimicrobial resistance profile [hazard ratio (HR) = 1.095 per any additional antimicrobial category, 95% confidence interval (CI) 1.018–1.178; $P = 0.014$] and infection with *P. aeruginosa* (HR = 2.08, 95% CI 1.11–3.88; $P = 0.022$) were independent predictors of late mortality. Other significant factors included Charlson comorbidity index and length of hospitalisation after the index blood culture.

Conclusion: Patients with GNB have a poor long-term prognosis. Risk factors for greater mortality at 1 year include co-morbidity, length of hospitalisation, and infecting organism and its resistance profile.

1. Introduction

Gram-negative bacteraemia (GNB) is a common and significant cause of community- and hospital-acquired sepsis, leading to approximately 10 000 deaths in the UK annually [1]. Short-term survival is particularly poor, with meta-analyses suggesting that 15-20% of patients die within 30 days [2,3]. Early effective empirical antibiotic therapy is considered the cornerstone intervention for improving patient prognosis in the acute setting.

GNB is typically regarded as an acute illness, which results in either death or full recovery after adequate treatment. Therefore, despite the plethora of studies on short-term outcome (usually defined as death before 30 days) and associated risk factors [4–7], there are currently no studies looking at long-term outcomes in an unselected cohort of patients with GNB. Andria et al. studied 423 haemato-oncological patients with carbapenem-resistant GNB and reported a 1-year mortality rate as high as 74.7% [8]. Similarly, Perl et al. reported the long-term outcome of 100 patients with suspected Gram-negative sepsis, finding a mortality rate of 60% over 6 years [9]. In addition, some authors have described general cohorts

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https://doi.org/10.1016/j.jgar.2021.03.019

of bacteraemic patients with long-term follow-up [10–14]. However, extrapolating to the GNB cohort from these studies might not be accurate as they include infections with Gram-positive organisms. Moreover, all previous analyses invariably suffer from high proportions of missing data, making identification of risk factors more challenging. This is particularly true for registry-based studies [10,11].

Determining whether GNB is associated with long-term sequelae to patients is important as it will allow clinicians to prognosticate more accurately as well as address any modifiable risk factors, none of which have been described so far for GNB. It will also allow an estimation of the true burden of disease. This is particularly important given the evidence suggesting that sepsis is associated with excess long-term mortality and a sustained decrease in patient quality of life months to years after the infection episode [15].

The aim of this retrospective, observational cohort study was to determine the 1-year all-cause mortality rate of patients with GNB caused by *Escherichia coli, Klebsiella* spp. or *Pseudomonas aeruginosa* as well as the all-cause late mortality rate (death by any cause between Days 31–365 after the index blood culture is taken). The study also aimed to identify factors significant in predicting late mortality in patients with GNB caused by these species. All factors measured in this study were hypothesised to be significant.

2. Materials and methods

2.1. Ethics

This project was determined to be a service evaluation by the Frimley Health NHS Foundation Trust Research and Development Department, therefore no formal National Health Service (NHS) Health Research Authority approval was sought.

2.2. Setting and study population

This study was conducted in Wexham Park Hospital, a 600-bed district general hospital in Berkshire, England, which provides acute hospital services including cardiology, maternity, stroke, surgery and emergency to a large and diverse population of more than 450 000 people, mainly of British, Middle Eastern, Asian and Polish ethnicity.

All cases of *E. coli, Klebsiella* and *P. aeruginosa* bacteraemia between 1 April 2017 and 31 March 2019 were included. Cases were identified through the mandatory Public Health England (PHE) surveillance reporting system. Patient data were retrieved from the hospital's electronic databases by information analysts, pooled and manually validated by two investigators. During data collection, investigators were blinded to patient outcome. Exclusion criteria included patients younger than 18 years old, polymicrobial infections containing Gram-positives, anaerobes or fungi (but not bacteraemias where all organisms were Gram-negative), and recurrent bacteraemia within 1 month. Patients who died within 30 days of infection were also excluded during analysis for late mortality risk factors. No power calculation was performed as the effect of multiple variables was examined simultaneously and few studies were available to guide us with regard to the magnitude of effect of each variable in the context of late mortality in GNB, for an accurate calculation. Moreover, the maximum number of eligible patients was included given that mandatory reporting of *P. aeruginosa* and *Klebsiella* bacteraemias was instituted by PHE in 2017. This study has been reported in accordance with the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines for observational studies.

2.3. Outcomes

The primary outcome was all-cause mortality between Days 31 and 365 from the day the index blood culture (BC), confirmed through the hospital information system, which includes post-discharge deaths.

2.4. Definitions

Polymicrobial bacteraemia was defined as the growth of more than one micro-organism in a BC. Source of infection was defined according to US Centers for Disease Control and Prevention (CDC) criteria [16] and categorised a low inoculum (urinary tract infection, central venous catheter infection) or high inoculum (all others), as described in the bloodstream infection mortality risk score (BSIMRS) [17]. Hospital-onset infections were defined as those detected ≥48 h after admission to hospital. Length of hospital stay was measured from the day of the index BC until the day of hospital discharge or inpatient death. Co-morbidity burden was assessed using the age-adjusted Charlson comorbidity index (CCI) [18]. Severity of disease was assessed using C-reactive protein (CRP), white blood cell (WBC) count (both collected at the time of the BC or within 24 h) and level of lactate collected within 4 h of the BC. The effectiveness of the empirical antimicrobial regimen at the time when the BC was taken was assessed by four independent assessors, blinded to patient outcome, to reach a consensus, as previously described [19]. The decision was guided by in vitro susceptibility results.

In vitro susceptibility of isolated clinical pathogens was determined using a VITEK®2 system according to European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints. For *E. coli* and *Klebsiella*, susceptibility to the following antimicrobial categories was tested: aminoglycosides (gentamicin, amikacin and tobramycin); antipseudomonal penicillins plus β-lactamase inhibitors (piperacillin/tazobactam); carbapenems (ertapenem and meropenem); non-extended-spectrum cephalosporins (cefuroxime); extended-spectrum cephalosporins (cefotaxime and ceftazidime); cephamycins (cefoxitin); fluroquinolones (ciprofloxacin); glycylcyclines (tigecycline); monobactams (aztreonam); penicillins (ampicillin); and penicillins plus β-lactamase inhibitors (amoxicillin/clavulanic acid). For *P. aeruginosa*, susceptibility to the following antimicrobial categories was tested: aminoglycosides (gentamicin, amikacin and tobramycin); antipseudomonal carbapenems (meropenem); antipseudomonal cephalosporins (ceftazidime); antipseudomonal fluoroquinolones (levofloxacin and ciprofloxacin); antipseudomonal penicillins plus β-lactamase inhibitors (ticarcillin/clavulanic acid and piperacillin/tazobactam); and monobactams (aztreonam). Multidrug resistance was defined as resistance to three or more prespecified antimicrobial categories according to recommendations from the European Centre for Disease Prevention and Control (ECDC) [20].

2.5. Statistical analysis

Multivariable Cox regression was used for survival analysis in IBM SPSS Statistics v.25.0 (IBM Corp., Armonk, NY, USA). Parameters for the model were chosen by initially taking into account the statistical significance of univariate comparisons, which was subsequently enhanced by clinical judgement and knowledge of known risk factors from the literature for long-term outcome of other infections [10–14]. Fisher's exact test, Student's *t*-test and Kruskal–Wallis test were used to univariably compare variables as appropriate. To replace missing data in WBC count (4.6%) and lactate level (22.9%), 25 multiple imputations were performed [21]. A prespecified sensitivity analysis was also performed using complete case analysis. No subgroup analyses were conducted owing to the small

Table 1
Baseline characteristics of patients included in the late mortality analysis.

Clinical factor	Entire cohort (N = 646)	Survivors (N = 503)	Non survivors (N = 143)	P-value[a]
Age (years) (mean ± S.D.)	71.7 ± 16.1	70.2 ± 16.2	77.1 ± 14.7	<0.001
Sex [n (%)]				
Male	334 (51.7)	251 (49.9)	83 (58.0)	0.089
Female	312 (48.3)	252 (50.1)	60 (42.0)	
CCI [median (IQR)]	5 (3–7)	4 (3–6)	6 (5–8)	<0.001
Infecting bacterium [n (%)]				
Escherichia coli	503 (77.9)	403 (80.1)	100 (69.9)	0.005
Klebsiella spp.	80 (12.4)	59 (11.7)	21 (14.7)	
Pseudomonas aeruginosa	34 (5.2)	22 (4.4)	12 (8.4)	
Polymicrobial	29 (4.5)	19 (3.8)	10 (7.0)	
Infection onset [n (%)]				
Hospital	85 (13.2)	60 (11.9)	25 (17.5)	0.093
Community	561 (86.8)	443 (88.1)	118 (82.5)	
Infection source				
High inoculum	266 (41.2)	196 (39.0)	70 (49.0)	0.034
Low inoculum	380 (58.8)	307 (61.0)	73 (51.0)	
Lactate (mmol/L) (mean ± S.D.)[b]	2.17 ± 1.42	2.08 ± 1.23	2.49 ± 1.96	0.047
CRP (mg/dL) (mean ± S.D.)	135 ± 112.8	135.9 ± 117.2	131.7 ± 95.9	0.660
WBC count (× 10^9 cells) (mean ± S.D.)[b]	13.4 ± 7.8	13.2 ± 6.8	14.2 ± 10.6	0.268
Effective treatment at the time of BC [n (%)]	480 (74.3)	376 (74.8)	104 (72.7)	0.665
LOS (days) (mean ± S.D.)	15.78 ± 19.76	14.07 ± 18.7	21.78 ± 21.7	<0.001
No of antimicrobial categories with resistance [median (IQR)]	1 (0–3)	1 (0–3)	2 (1–4)	0.016

S.D., standard deviation; CCI, Charlson comorbidity index; IQR, interquartile range; CRP, C-reactive protein; WBC, white blood cell; BC, blood culture; LOS, length of stay in hospital after index BC.
[a] Univariate comparisons and associated P-values should not be interpreted as true correlations as they are subject to significant confounding.
[b] Includes imputed values.

sample size of possible individual subgroups. The level of statistical significance was set at 0.05.

3. Results

A total of 881 patients developed GNB during the study period. According to the exclusion criteria, children (n = 18), polymicrobial infections (n = 36), recurrent bacteraemias (n = 11), samples sent from different institutions (n = 3) and patients with missing data on the antimicrobial regimen (n = 24) were excluded, leaving 789 patients for the mortality analysis. Overall, 36.2% of patients (286/789) died within 1 year of GNB detection. This included 143 patients (18.1%) who suffered early mortality (before 30 days) and 143 patients who suffered late mortality (between Days 31 and 365). The former group of patients was excluded: it has been described together with associated risk factors for early mortality in a separate publication [19]. In the end, 646 patients were included in the final analysis for late mortality risk factors.

In the final cohort, the average age was 71.7 years with an equal sex distribution (51.7% male and 48.3% female) (Table 1). *Escherichia coli* was the most prevalent pathogen (77.9%), followed by *Klebsiella* (12.4%), *P. aeruginosa* (5.2%) and polymicrobial infections (4.5%). The majority of infections were community-acquired (86.8%) and originated from a low-inoculum source (58.8%). Effective empirical antibiotics at the time of the BC were given in 74.3% of cases. Full resistance profiles were available for all patients (Table 2). Differences in baseline characteristics between patients who suffered late mortality versus patients who did not, with associated univariate comparisons, are shown in Table 1.

In the multivariable survival analysis, an adverse antimicrobial resistance profile was independently associated with greater late mortality [hazard ratio (HR) = 1.095 per any additional antimicrobial category, 95% confidence interval (CI) 1.018–1.178; P = 0.014] (Table 3). No antimicrobial category individually, nor extended-spectrum β-lactamase (ESBL) or multidrug-resistant (MDR) status, were found to be significant (data not shown). Patients with *P. aeruginosa* infection were at greater risk for adverse outcome (HR = 2.08, 95% CI 1.11–3.88; P = 0.022) (Fig. 1). Patients with *Klebsiella* or polymicrobial infections also demonstrated an increased risk, but the difference was not statistically significant (Table 3). Other factors associated with greater mortality were an increased CCI (HR = 1.12 per point higher, 95% CI 1.048–1.196; P = 0.001) as well as prolonged admission after the index bacteraemia (HR = 1.008 per additional day, 95% CI 1.002–1.014; P = 0.005). Effective antimicrobial treatment at the time of the BC was found to be protective, but the observed HR was not statistically significant (HR = 0.72, 95% CI 0.48–1.08; P = 0.111). There was no significant association between late mortality and age, sex, lactate level, or source and onset of infection (Table 3). CRP level and WBC count were similar between the two groups and are not described to be associated with long-term adverse outcome in infection [10–14]. Therefore, they were not included in the final multivariable model. Sensitivity analysis showed similar results for complete cases and cases with imputed values.

4. Discussion

This retrospective study of a general cohort of patients with GNB thoroughly details all-cause mortality rates and risk factors for late mortality over a 1-year follow-up period. To the best of our knowledge, this is the first study in this particular field. Our study cohort had a more guarded 1-year prognosis (36.2%) than previously described all-cause bacteraemia cohorts (25–30.7%) [10,12] but a more favourable one than cohorts with *Staphylococcus aureus* (47.5%) [14] or carbapenem-resistant GNB (74.7%) [8] It should be noted, however, that most of these previous studies describe cohorts more than 5–10 years ago when clinicians had reduced awareness of sepsis and lacked access to current advances in critical care and new antimicrobials, making direct comparisons difficult.

We have demonstrated that long-term outcome in patients with GNB is poor and comparable with that of non-communicable diseases that are typically associated with adverse long-term sequalae. For example, 1-year all-cause mortality following myocardial infarction or stroke has been reported to be ~12%, which is much more favourable than GNB [22,23]. This is true even for older patients, with similar age ranges to those in our study [24]. Despite that, these conditions are often highlighted first in the medi-

Table 2
Resistance profiles of isolated pathogens.

Antimicrobial category	% resistant *Escherichia coli*	*Klebsiella* spp.	*Pseudomonas aeruginosa*
Penicillins	65.1	100	N/A
Penicillins + BLIs	32.2	22.5	N/A
Non-extended-spectrum cephalosporins	24.3	20.2	N/A
Extended-spectrum cephalosporins[a]	17.4	12.4	2.7
Antipseudomonal penicillins + BLIs	9.1	19.1	20.5
Carbapenems	0.2	3.4	10.3
Fluroquinolones[b]	25.7	19.1	10.2
Aminoglycosides	16.6	13.5	5.1
Cephamycins	11	9	N/A
Monobactams	17.2	11.2	87.2
Glycylcyclines	0	3.75	N/A

BLI, β-lactamase inhibitor; N/A, not applicable.
[a] Ceftriaxone for *E. coli*/*Klebsiella* and ceftazidime for *P. aeruginosa*.
[b] Ciprofloxacin for *E. coli*/*Klebsiella* and ciprofloxacin and levofloxacin for *P. aeruginosa*.

Table 3
Factors associated with risk of late mortality in multivariable analysis.

Variable	HR	95% CI	*P*-value
No of antimicrobial categories with resistance (per additional category)	1.095	1.018–1.178	0.014
Bacterium[a]			
Klebsiella spp.	1.30	0.80–2.10	0.288
Pseudomonas aeruginosa	2.08	1.11–3.88	0.022
Polymicrobial	1.14	0.58–2.24	0.699
Treatment at the point of the BC (effective vs ineffective)	0.72	0.48–1.08	0.111
Infection source (high- vs. low-inoculum)	1.25	0.89–1.77	0.195
Infection onset (hospital vs. community)	1.13	0.71–1.82	0.608
Age (per year older)	1.005	0.90–1.21	0.492
Lactate (per mmol/L higher)	1.08	0.96–1.22	0.283
CCI (per point higher)	1.12	1.048–1.196	0.001
Sex (male vs. female)	0.95	0.67–1.34	0.774
LOS (per additional day)	1.008	1.002–1.014	0.005

HR, hazard ratio; CI, confidence interval; BC, blood culture; CCI, Charlson comorbidity index; LOS, length of stay in hospital after index BC.
[a] *Escherichia coli* as baseline.

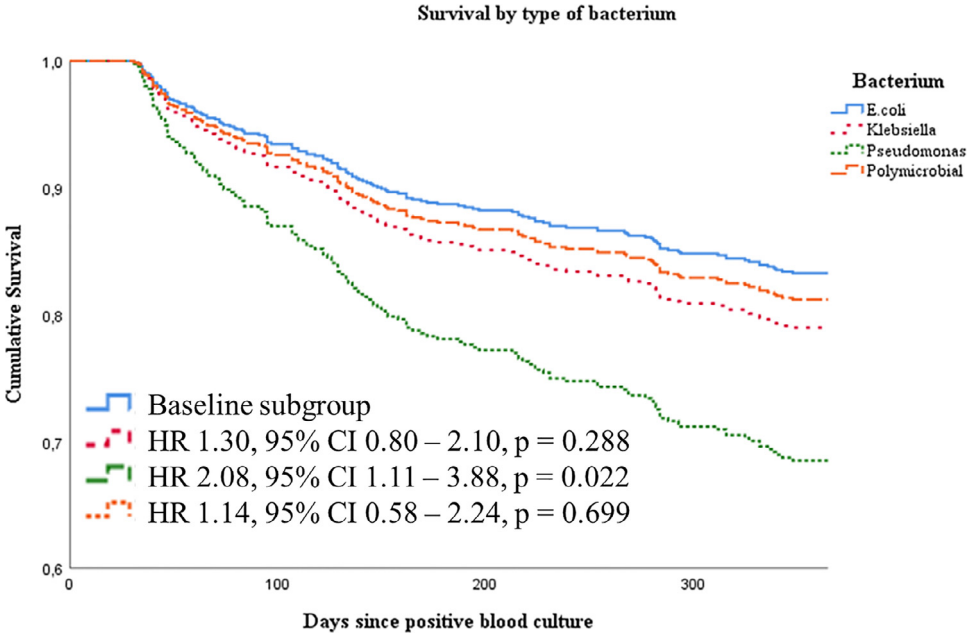

Fig. 1. One-year survival graph of patients who did not die within 30 days of bacteraemia detection by type of bacterium. Results adjusted for age, sex, onset of infection, source of infection, Charlson comorbidity index, lactate level, length of hospital stay post-detection of bacteraemia, antibiotic treatment at the time when the blood culture was taken, and number of antimicrobial categories with resistance. HR, hazard ratio; CI, confidence interval.

cal history, while previous episodes of GNB are almost never mentioned. We propose that GNB constitutes a significant independent co-morbidity and represents more than an acute illness, with long-lasting effects on patient outcome. This is likely because infection or colonisation with Gram-negative bacteria has been shown to increase the risk of subsequent recurrent infection within 1 year, especially if multidrug resistance is present [25]. This result is in agreement with our finding that a more severe antimicrobial resistance pattern is associated with greater mortality.

In our study, *P. aeruginosa* infection was associated with greater late mortality, an unsurprising finding. *Pseudomonas aeruginosa* is known to persist through the development of biofilms and often demonstrates a multiresistant profile, making eradication of infection challenging [26]. Infection is also more common in the context of immunocompromise, haematological malignancy and foreign devices, making it a surrogate marker for severe co-morbidity [26]. Our results should alert clinicians that *P. aeruginosa* bacteraemia carries a highly adverse long-term prognosis even after successful treatment of the initial infection episode. Other factors highlighted were the CCI, which is commonly used to predict 10-year mortality [18], and the length of hospital stay, which likely represents a proxy for frailty. Interestingly, the age adjustment in the CCI neutralised the effect of age on mortality. We did not find a statistically significant effect of effective antibiotic treatment on late mortality, although the HR was suggestive of a protective impact. Our study was likely underpowered to show such difference as the magnitude of the effect was small. Ideally, prospective cohort studies with an internal control should be conducted to better evaluate this potentially modifiable factor.

Our study has noticeable strengths. It has a larger number of participants than most studies in the field of GNB with no loss to follow-up. The rate of missing data is low (2.4%) and blinding of investigators was applied where possible. We adjusted for clinically significant confounding factors such as patient co-morbidities, severity of disease, and the effectiveness of the antimicrobial regimen used to treat the initial infection [27]. The latter is particularly uncommon in long-term studies, especially registry studies.

Limitations include the retrospective design as well as the fact that it is a single-centre study. This could limit the generalisability of our results, especially to settings with higher proportions of antimicrobial resistance. We did not have susceptibility results for some antimicrobial categories suggested for testing by the ECDC [20] as our laboratory does not routinely test for them due to their lack of clinical use in GNB in our setting. These included anti-methicillin-resistant *S. aureus* (anti-MRSA) cephalosporins (ceftaroline), phenicols (chloramphenicol), trimethoprim/sulfamethoxazole, phosphonic acids (fosfomycin), polymyxins (colistin) and tetracyclines (doxycycline). This might have led to misclassification of some strains as non-MDR and therefore to a non-statistically significant result. With regard to our result about additional antimicrobial categories having an adverse effect on late mortality though, we are confident that having extra data would have increased granularity and therefore the statistical significance of the results, rather than having the opposite effect. Misclassification might have also happened due to the increase in EUCAST amoxicillin/clavulanic acid breakpoints in 2018 but should have evenly affected patients in both groups. It should also be noted that we examined all-cause mortality of patients rather than infection-specific causes of death. It has been shown that most patients with bacteraemia die from non-infectious causes in the year following the infection [11,12]. The interplay between bacteraemia and these subsequent events is currently unknown.

In conclusion, this study informs clinicians that GNB carries an unfavourable long-term prognosis, with more than one-third of patients dying within 1 year. It identifies a previously undescribed magnitude of impact of an acute GNB on mortality as well as its association with antimicrobial resistance and host co-morbidities. This information allows better prognostication for patients. It also drives the development of robust early microbiological diagnostic methodology and high antimicrobial stewardship and infection control standards, which are an integral element of delivering high-quality care.

Acknowledgments

Full list of contributors: Alexander Aiken, Jennifer Wyeth, Cereus Harry, Victoria Gentry, David O'Dowd, Charles Savin and Louise Mcgovern.

Funding

No funding was required for the conduction of this study. Funding for OpenAccess publication of the results was provided by the University College London Library after completion of the study and after acceptance of the study for publication.

Competing interests

None declared.

Ethical approval

Not required.

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