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Practice points

Clinical risk stratification and antibiotic management of NDM and OXA-48 carbapenemase-producing Enterobacteriaceae bloodstream infections in the UK

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The treatment choices for bloodstream infections (BSIs) caused by carbapenemase-producing Enterobacteriaceae (CPE) are limited. Clinical management must take into account drug toxicities and antimicrobial stewardship principles. The ability to accurately identify patients at risk of developing CPE-associated BSI is important for patient management and guidance of early appropriate therapy. One such scoring system, the Giannella risk score, uses parameters including CPE colonization, recent surgery, and chemo/radiotherapy [1]. For optimizing treatment and minimizing antimicrobial side-effects, clinical studies validating the INCREMENT-CPE score (aggregating factors including presence of shock, Pitt bacteraemia score, Charlson comorbidity score, site of sepsis and early targeted therapy) have demonstrated a role for directed monotherapy in low-risk patients with CPE-associated BSI [2]. We undertook a retrospective study of all CPE-associated BSIs admitted to Imperial College Healthcare NHS Trust between 2015 and 2017 in order to evaluate the potential utility of Giannella risk score and INCREMENT risk score.

Baseline clinical and microbiological characteristics of the group are shown in Table I. Of the 21 patients with a CPE-associated BSI, NDM-producing *Klebsiella pneumoniae* (43%) and OXA-48-producing *K. pneumoniae* (33%) were most commonly isolated. There were no bloodstream isolates of KPC-producing *K. pneumoniae*, reflecting local epidemiology [3]. Eleven isolates underwent colistin sensitivity through broth microdilution testing, of which none was resistant. The underlying comorbidities were haematological (29%), urological (29%), and hepatobiliary (24%) conditions. Ten patients (48%) were known to carry corresponding CPE isolates at least a week before onset of BSI: use of this information resulted in five (24%) patients receiving appropriate empirical therapy. Of these ten patients known to be colonized prior to BSI onset, the majority, eight cases (80%), had a high Giannella risk score ($\geq$2).

All (21/21) patients were commenced on targeted, dose-optimized combination therapy based on identification and in-vitro (EUCAST disc) sensitivities obtained within 48 h of blood cultures being obtained, consisting of either two or three antimicrobials. Eighteen patients had a meropenem backbone to definitive therapy (2 g every 8 h, renally adjusted) and 13 received colistin (9 million units loading, and 3 million units every 8 h maintenance, renally adjusted). Additional agents included tigecycline (10), aztreonam (two), amikacin (three), gentamicin (two), ciprofloxacin (one), according to susceptibilities. In 14/21 cases the regimen contained two or more agents active *in vitro* and in 7/21 cases only a single agent was

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Table I
Baseline characteristics, risk scoring, and antibiotic management according to 30-day inpatient mortality ($N = 21$)

Variable	Patients alive at day 30 after onset of BSI (%)	Patients who died by day 30 after onset of BSI (%)	*P*-value
No. (%)	13 (62%)	8 (38%)	
Age, median (IQR)	66 (65–71)	64 (61–75)	NS
Female sex	5/13	4/8	NS
Organism isolated			NS
Klebsiella pneumoniae	8	7	
Escherichia coli	2	1	
Enterobacter cloacae	2	0	
Citrobacter freundii	1	0	
Resistance mechanism			
NDM	7 (33%)	5 (24%)	NS
OXA-48	6 (29%)	2 (10%)	
NDM and OXA-48	0	1 (5%)	
Pitt bacteraemia score, median (IQR)	2 (1–2)	2 (1–3)	NS
Charlson comorbidity score, median (IQR)	3 (2–4)	8 (5–8)	<0.01
Giannella risk score ≥2 (out of 10 patients with known CPE carriage prior to onset of BSI)	3/7	2/3	NS
INCREMENT-CPE score			
Low risk (<8)	9 (43%)	4 (19%)	NS
High risk (≥8)	4 (19%)	4 (19%)	
Increase in serum creatinine ≥2-fold	5 (24%)	2 (10%)	NS
Increase in alanine transaminase ≥3-fold	2 (10%)	1 (5%)	NS
Meropenem MIC, median (mg/L)	2	6	NS

BSI, bloodstream infection; IQR, interquartile range; NS, non-significant ($P > 0.05$); CPE, carbapenemase-producing Enterobacteriaceae; MIC, minimum inhibitory concentration.

active against the isolate. All treatment continued for a minimum of 14 days unless the patient died.

Potential adverse events relating to antimicrobial use included a two-fold serum creatinine rise from baseline in 7/13 (54%) patients treated with a high-dose colistin, and alanine transaminase rise of >3 times upper limit of normal in 3/18 (17%) patients treated with meropenem. Early 14-day mortality was 6/21 (29%) and 30-day mortality was 8/21 (38%), comparable with other studies [4]. Of the five patients with an NDM-producing isolate who died, two had CPE with meropenem minimum inhibitory concentration (MIC) ≥32 mg/L. There was a statistically non-significant difference in meropenem MIC between isolates from patients who died and survived. When INCREMENT scoring was applied, 30-day mortality was 4/13 (31%) patients in the low-risk group and 4/8 (50%) in the high-risk group, but this did not reach statistical significance (χ^2-test: $P = 0.38$). The Charlson comorbidity score was significantly higher in patients who died compared to those who survived at day 30 (Mann–Whitney test: $P < 0.01$). These outcomes suggest that while INCREMENT score may be useful for identifying patients whose therapy can be rationalized, the Charlson comorbidity score was associated with mortality in our group, although this may be subject to confounding.

The experience within our centre was unique as there was a higher incidence of OXA-48- and NDM-producing isolates. Previous studies have predominantly focused on infection by KPC-producing *K. pneumoniae* infections [5]. Treatment was associated with possible drug toxicities and we explored the role of INCREMENT score in identifying patients suitable for monotherapy. Although there was a lower 30-day mortality in the low-risk group, we advise caution in use of the INCREMENT score for settings similar to ours [6]. The original derivation cohort consisted of a much lower frequency of MBL-producing isolates compared to our group (10% vs 62% respectively) and further study is required.

All patients were started on combination antimicrobial therapy on, or before, the identification of CPE-associated BSI. It is possible that knowledge of local epidemiology biased clinical decisions to commence combination therapy at BSI onset. Screening strategies employed at our trust led to the identification of CPE carriage of 10/21 patients at least a week prior to the onset of CPE-associated BSI. This colonization knowledge led to earlier, targeted antimicrobial therapy for five haematology patients. We note the sensitivity of the Giannella risk score in identifying high-risk colonized patients for our group, suggesting a possible future role in risk stratification and improving commencement of early targeted therapy.

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Conflict of interest statement

J.A.O. is a consultant for Gama Healthcare and has consulted for Pfizer in the last three years. The other authors declare no conflicts of interest.

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References

[1] Giannella M, Trecarichi EM, De Rosa FG, Del Bono V, Bassetti M, Lewis RE, et al. Risk factors for carbapenem-resistant *Klebsiella pneumoniae* bloodstream infection among rectal carriers: a prospective observational multicentre study. Clin Microbiol Infect 2014;20:1357—62.

[2] Gutiérrez-Gutiérrez B, Salamanca E, de Cueto M, Hsueh PR, Viale P, Paño-Pardo JR, et al. Effect of appropriate combination therapy on mortality of patients with bloodstream infections due to carbapenemase-producing Enterobacteriaceae (INCREMENT): a retrospective cohort study. Lancet Infect Dis 2017;17:726—34.

[3] English Surveillance Programme for Antimicrobial Utilisation and Resistance (ESPAUR) Report. Public Health Engl 2017:1—143.

[4] Papadimitriou-Olivgeris M, Fligou F, Bartzavali C, Zotou A, Spyropoulou A, Koutsileou K, et al. Carbapenemase-producing *Klebsiella pneumoniae* bloodstream infection in critically ill patients: risk factors and predictors of mortality. Eur J Clin Microbiol Infect Dis 2017;36:1125—31.

[5] Cano A, Gutiérrez-Gutiérrez B, Machuca I, Gracia-Ahufinger I, Pérez-Nadales E, Causse M, et al. Risks of infection and mortality among patients colonized with *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae*: validation of scores and proposal for management. Clin Infect Dis 2018;66:1204—10.

[6] Boyd SE, Moore LSP, Rawson TM, Hope WW, Holmes AH. Combination therapy for carbapenemase-producing Entero-bacteriaceae: INCREMENT-al effect on resistance remains unclear. Lancet Infect Dis 2017;17:899—900.