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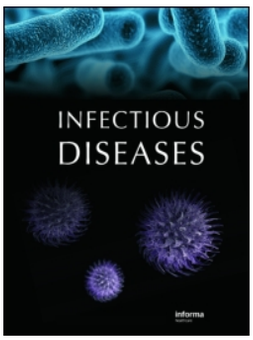

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ORIGINAL ARTICLE

Epidemiology and outcome of infections with carbapenem-resistant Gram-negative bacteria treated with polymyxin B-based combination therapy

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Abstract

Introduction: Infections with carbapenem-resistant Gram-negative bacteria (CRGNB) are increasing and are associated with a high mortality. Synergistic effects of combination therapy with a polymyxin, carbapenem, and rifampin have been observed in *in vitro* studies. Clinical data are limited to retrospective studies. *Methods:* We performed an observational cohort study of patients over 18 y of age who were treated with polymyxin B combination therapy. *Results:* One hundred and four patients were studied. The mean age was 77 y; 73% had recently received antibiotics, 67% had recently been hospitalized, and 47% lived in a nursing facility. The most common infections were pneumonia and urinary tract infection due to Acinetobacter baumannii (33%), Klebsiella pneumoniae (24%), and Pseudomonas aeruginosa (11%). Treatment regimens included polymyxin B with a carbapenem in 48%, with additional rifampin in 23%. Clinical success was achieved in 50% and reinfection occurred in 25%. Treatment-related acute renal failure occurred in 14.4%. No treatment-related hemodialysis was needed. All-cause hospital mortality was 47% and mortality after 6 months was 77%. No significant difference was found between treatment regimens. Age (odds ratio (OR) 10.4 per 10 y, $p = 0.04$), severity of acute illness (OR 2.2 per point, $p < 0.001$), and Charlson score (OR 1.12 per point, $p = 0.04$) were associated with hospital mortality. K. pneumoniae was associated with increased hospital survival compared to other CRGNB ($p = 0.03$). *Conclusion:* CRGNB infections are associated with previous antibiotic and health care exposure. Mortality is related to age and the severity of chronic and acute illness.

Keywords: *Carbapenem resistance, Gram-negative bacteria, polymyxin B*

Introduction

Infections due to carbapenem-resistant Gram-negative bacteria (CRGNB) are an increasing global problem [1–3]. These infections are associated with a high mortality, prolonged hospital stay, and high health care costs [4,5]. Reported mortality rates vary from 47% to 66% [2,6]. The most commonly identified multidrug-resistant Gram-negative bacteria are Klebsiella pneumoniae, Pseudomonas aeruginosa, and Acinetobacter baumannii. Due to increasing carbapenem resistance, the use of polymyxin B and colistin (polymyxin E) has increased. Their use fell out of favor in the 1970s due to unfavorable side effects, mainly nephrotoxicity and neurotoxicity.

Polymyxin B and colistin are bactericidal agents acting on lipopolysaccharide (LPS) on the bacterial cell wall and on the outer membrane, with a detergent-like action. Most clinical experience involves colistin use. Incomplete data exist regarding the pharmacodynamics (PD) and pharmacokinetics (PK) of colistin, and little is known about polymyxin B. However, a recently published study showed that polymyxin B, unlike colistin, is not cleared renally and therefore dosing should not be adjusted for renal dysfunction [7,8].

Observational studies have shown a greater than 98% sensitivity of CRGNB to polymyxins. However, due to increased polymyxin use, resistant strains are

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emerging, especially in Latin America, Greece, and Asia [3].

Synergistic effects of combination therapy consisting of a polymyxin with a carbapenem and rifampin have been observed in *in vitro* studies [9–12]. However, in a recently reported multicenter randomized clinical trial, the addition of rifampin to colistin in the treatment of extensively drug-resistant A. baumannii infections did not result in improved mortality or reduced length of hospitalization compared to colistin alone [13]. Clinical data to support the superiority of combination therapy are limited to retrospective reviews evaluating bacteremia and mainly involve colistin [14,15].

We performed an observational cohort study of various CRGNB infections to further study risk factors, outcomes, and toxicity of polymyxin B combination therapy.

Materials and methods

Study design

A prospective observational cohort study was performed from November 2009 to November 2010 in a 700-bed community teaching hospital in Brooklyn, New York. All patients older than 18 y with an infection with a carbapenem-resistant K. pneumoniae, P. aeruginosa, or A. baumannii, who were treated with polymyxin B combination therapy for 3 or more days, were included. The research team was notified by the pharmacy when polymyxin B therapy was initiated by the primary team. The decision to start polymyxin B treatment was made by an independent infectious diseases specialist. Infection was defined as a clinical deterioration, i.e. meeting systemic inflammatory response syndrome (SIRS) criteria [16], with localizing symptoms and/or signs in combination with a site-specific positive culture with a CRGNB. Definitions are provided in more detail below.

Patients without signs of active infection (i.e. with CRGNB colonization) were excluded. All patients were treated with a loading dose of 25,000 IU/kg of polymyxin B, followed by 25,000 IU/kg/day in divided doses, with dose adjustment for glomerular filtration rate (GFR) less than 50 ml/min [17]. As an additional agent, a carbapenem with or without 600 mg of daily rifampin was mostly used, despite resistance to the additional agent. In 9 cases, ampicillin/sulbactam was used in lieu of a carbapenem for infections with A. baumannii with intermediate sensitivity to the sulbactam component of this agent. In 15 cases, tigecycline was used for similar reasons. The decision to use rifampin for either organism was made by the independent infectious diseases consultant. Patients were followed until discharge or death. Mortality was reviewed again after 6 months through evaluation of hospital records and contact by phone.

Microbiology

All isolates were identified in the microbiology laboratory of our institution. Only infections with K. pneumoniae, P. aeruginosa, or A. baumannii resistant to all penicillins, cephalosporins, quinolones, macrolides, tetracyclines, aminoglycosides (gentamicin and amikacin), and carbapenems (imipenem and meropenem) were included. Susceptibility was determined by automated method (Vitek, bioMérieux, Marcy l'Etoile, France). Results were interpreted in accordance with 2009 Clinical and Laboratory Standards Institute (CLSI) criteria [18]. A modified Hodge test was performed to confirm carbapenem resistance. Polymyxin B sensitivities were not performed, as official breakpoints are not available.

Definitions and data collection

An isolate was labeled CRGNB if it tested resistant to all antibiotic classes as mentioned above. Infection was defined as meeting SIRS criteria with clear site-specific symptoms and/or signs. Pneumonia was defined by the presence of increased sputum production, increased oxygen requirement, positive respiratory cultures, and an infiltrate on imaging. Urinary tract infection (UTI) required dysuria, polyuria, or flank pain, or suggestive imaging for pyelonephritis in the presence of pyuria and positive cultures. If a catheter was present, urine samples were collected after placement of a new catheter. Bacteremia was defined by the growth of bacteria in the blood. Skin and soft infection (SSTI) was defined as the presence of cellulitis and purulence with positive tissue cultures. Osteomyelitis was defined by positive bone cultures, consistent imaging, and evidence of osteomyelitis on surgical or pathological examination. Demographic and baseline medical history were recorded: exposure to antibiotics within 6 months prior to infection, hospitalization within 6 months prior to infection, immunosuppression (i.e. receiving immunosuppressive agents including >10 mg prednisone for 1 month, infection with HIV, neutropenia), malignancy, presence of mechanical ventilation or tracheostomy at the time of infection, and Charlson co-morbidity index [19]. The onset of infection was considered as the date of a positive culture with a CRGNB. Severity of disease was evaluated with the Acute Physiology and Chronic Health Evaluation IV (APACHE IV) score in intensive care unit (ICU) patients [20]. Sepsis was defined as meeting the Society of Critical Care Medicine (SCCM) and

American College of Chest Physicians (ACCP) criteria [16]. Shock was defined as a requirement for vasopressors to maintain a mean arterial pressure >60 mmHg; respiratory failure was defined as the need for mechanical ventilation. Renal insufficiency and renal failure were defined as meeting the injury and failure criteria of the RIFLE classification [21]. Encephalopathy was defined as a Glasgow Coma Scale (GCS) score less than 11. Disseminated intravascular coagulation (DIC) was defined as thrombocytopenia and elevated activated partial thromboplastin time and prothrombin time, without the presence of another etiology. Myocardial infarction was defined by a troponin >1 ng/ml, and hyperglycemia was defined by a fasting glucose >200 mg/dl. The acute illness score was defined as the sum of each of the following: shock, respiratory failure, acute renal failure (ARF), myocardial infarction, and encephalopathy, allocating 1 point to each.

The outcomes measured were: all-cause hospital mortality, all-cause mortality at 6 months, clinical success, microbiological success, and ARF secondary to treatment, which was defined by renal failure occurring after more than 48 h of treatment. Creatinine clearance was calculated with the Cockroft–Gault formula at baseline, day 2, day 4, day 7, at the end of treatment, and at discharge [22]. Clinical success was determined by the research team by resolution of signs of infection as stated above, improvement of relevant laboratory parameters for the site of infection, and discontinuation of antibiotics. Microbiological success was determined by clearance of the studied organisms from 2 successive cultures. Reinfections were defined as the presence of a CRGNB after at least 1 negative culture and initial clinical success.

Statistical analysis

Statistical analyses were carried out using IBM SPSS Statistics for Windows, version 19.0 (IBM Corp., Armonk, NY, USA). Univariate analyses were performed to evaluate all-cause hospital mortality, all-cause mortality at 6 months, clinical success, microbiological success, hospital length of stay (LOS), and treatment-related ARF. Hospital LOS was log-transformed prior to analysis because of its skewed distribution. Categorical predictor variables for the analysis included the bacterial species, source of infection, treatment regimen, use of rifampin, and diabetes. Numerical predictor variables included age, body mass index (BMI), and the Charlson comorbidity index. Additionally, the component score of a principal component analysis was used as a weighted index for the acute illness. This weighted score included shock, respiratory failure, ARF, myocardial infarction, and encephalopathy. Fisher's exact tests were used for analyses with both categorical predictors and outcome variables; 1-way analysis of variance (ANOVA) was used for categorical predictors and numerical outcome measures. Correlations were used for both numerical predictors and numerical outcome measures. Univariate logistic regression was used for numerical predictors and binary outcome measures. Significant effects of the univariate analyses were included in multivariate analyses to correct for dependencies among predictor variables.

Results

One hundred and four patients were studied. Patient characteristics at the time of diagnosis with a CRGNB infection are shown in Table I. At the time of isolation of a CRGNB, 59% of patients were mechanically ventilated and 35% had a tracheostomy. Ventilated patients were either admitted to the ICU or a specialized respiratory care unit. Table II specifies the infections, treatment regimens, and outcomes. A total of 15% of patients were bacteremic with CRGNB, and only 5% had isolated bacteremia. Most infections were caused by A. baumannii and nearly a third were due to a combination of CRGNBs. Complications of CRGNB infections are shown in Table III. Approximately 14% of patients progressed to renal failure

Table I. Patient characteristics at the time of diagnosis with carbapenem-resistant Gram-negative bacteria.

Characteristic	
Age, y, mean ± SD	77 ± 12.9
Male/female, *n*/*n*	62/42
Ethnicity, *n* (%)	
Caucasian	75 (72)
Hispanic	12 (11.5)
Asian	11 (10.6)
African American	6 (5.8)
BMI, kg/m^2, mean	26.9
Recent antibiotics, *n* (%)	76 (73.1)
Recent hospitalization, *n* (%)	70 (67.3)
Mechanical ventilation, *n* (%)	61 (58.7)
Skilled nursing facility resident, *n* (%)	49 (47.1)
Diabetes mellitus, *n* (%)	50 (48.1)
ICU admission, *n* (%)	38 (36.5)
Current tracheostomy, *n* (%)	36 (34.6)
Immunosuppression, *n* (%)	13 (12.5)
Hemodialysis dependent, *n* (%)	6 (5.8)
LOS prior to infection, days, mean ± SD	16 ± 15
Charlson score, mean ± SD	8.12 ± 3.8
APACHE IV score, mean ± SD[a]	20

SD, standard deviation; BMI, body mass index; ICU, intensive care unit; LOS, length of stay; APACHE IV, Acute Physiology and Chronic Health Evaluation IV.
[a]Calculated for ICU patients only.

Table II. Outcomes of infections with carbapenem-resistant Gram-negative bacteria.

	Clinical success (CS), %	Days to CS, mean (SD)	Microbiological success, %	Hospital LOS, days, mean (SD)	ICU LOS, days, mean (SD)	ARF due to treatment, %	Hospital mortality, %	6-month mortality, %
Pneumonia ($n = 37$)	47.2	16.6 (8.3)	45.9	52.3 (30.1)	21.2 (16.8)	10.8	48.6	64.7
UTI ($n = 17$)	82.4	10.2 (7.14)	52.9	26.9 (25.7)	17.5 (17.7)	0	17.6	56.3
SSTI + OM ($n = 10$)	50.0	9 (7.1)	/	67.4 (64.8)	/	10.0	40.0	62.5
Bacteremia ($n = 5$)	20.0	8 (/)	40.0	76.6 (50.3)	5	40.0	60.0	100.0
Multiple sites ($n = 35$)[a]	28.6	15.6 (9.9)	37.1	66.0 (49.7)	17.5 (13.0)	5.7	60.0	80.6
A. baumannii ($n = 34$)	44.1	16.8 (10.4)	46.8	53.3 (37.3)	19 (13.2)	14.7	50.0	65.6
K. pneumoniae ($n = 25$)	72.0	11.1 (6.2)	52.0	47.4 (50.1)	17.8 (16.7)	4.0	24.0	68.2
P. aeruginosa ($n = 11$)	50.0	10.3 (9.5)	20.0	51.0 (42.1)	23.5 (10.6)	0	50.0	60.0
Multiple CRGNB ($n = 34$)[b]	26.5	14.8 (8.7)	38.2	66.0 (44.9)	19.3 (18.0)	14.7	58.8	79.3
Polymyxin ($n = 6$)	33.3	9.5 (5.0)	33.3	29.5 (24.3)	32.7 (35.0)	0	66.7	80.0
Polymyxin + CP ($n = 50$)	38.0	13.6 (8.4)	44.0	64.1 (48.4)	17.4 (9.0)	8.0	54.0	80.4
Polymyxin + CP + rif ($n = 24$)	45.8	14.1 (7.2)	37.5	55.8 (42.0)	20.3 (16.0)	16.7	45.8	60.9
Polymyxin + amp/s ($n = 9$)	62.5	10.0 (4.9)	71.4	46.1 (34.9)	27.5 (13.2)	0	44.4	50.0
Polymyxin + CP + tig ($n = 15$)	66.7	15.3 (12.3)	33.3	41.7 (35.5)	11.2 (6.8)	20.0	20.0	54.5
Age < 65 y ($n = 16$)	62.5	17.3 (13.9)	50.0	61.8 (54.9)	30.6 (16.7)	12.5	25.0	40.0
Age 65–75 y ($n = 22$)	50.0	14.5 (7.9)	50.0	61.7 (49.5)	11.8 (9.2)	4.5	40.9	61.9
Age > 75 y ($n = 66$)	40.0	13.5 (5.2)	36.9	51.7 (38.8)	20.9 (15.9)	12.1	54.5	80.7
Charlson 0–5 ($n = 27$)	55.5	13.6 (11.0)	56.0	57.3 (53.0)	17.1 (14.5)	14.8	33.3	54.2
Charlson 6–10 ($n = 47$)	44.7	13.6 (7.0)	36.2	58.4 (43.5)	16.5 (8.3)	4.3	46.8	69.0
Charlson > 10 ($n = 30$)	37.9	14.7 (6.3)	40.0	48.9 (34.7)	23.5 (19.0)	16.7	60.0	85.2
AIS 0 + 1 ($n = 32$)	68.8	13.0 (10.0)	50.0	48.8 (44.5)	7.0 (8.5)	3.1	18.8	53.6
AIS 2 + 3 ($n = 39$)	37.8	12 (5.3)	47.4	68.4 (50.8)	12.6 (6.4)	18.4	55.3	75.8
AIS 4 + 5 ($n = 33$)	30.3	16.4 (7.6)	30.3	47.3 (30.4)	22.6 (16.6)	9.1	66.7	78.1

SD, standard deviation; LOS, length of stay; ICU, intensive care unit; ARF, acute renal failure; UTI, urinary tract infection; SSTI, skin and soft tissue infection; OM, osteomyelitis; CRGNB, carbapenem-resistant Gram-negative bacteria; CP, carbapenem; rif, rifampin; amp/s, ampicillin/sulbactam; tig, tigecycline; Charlson, Charlson score; AIS, acute illness score; /, data not available or unable to calculate.

[a]Pneumonia + UTI, $n = 15$; pneumonia + bacteremia, $n = 5$; pneumonia + SSTI/OM, $n = 7$; pneumonia + UTI + bacteremia, $n = 2$; UTI + bacteremia, $n = 2$; UTI + SSTI + bacteremia, $n = 1$; SSTI + bacteremia, $n = 1$; pneumonia + OM + bacteremia, $n = 1$; pneumonia + UTI + OM, $n = 1$.

[b]A. baumannii + P. aeruginosa, $n = 11$; A. baumannii + K. pneumoniae, $n = 14$; P. aeruginosa + K. pneumoniae, $n = 2$, A. baumannii + K. pneumoniae + P. aeruginosa, $n = 7$.

after more than 48 h of treatment with polymyxin B. Complete recovery of renal function occurred in 33% and no treatment-related hemodialysis was needed.

Univariate analysis showed that among the infections, UTI were associated with an increased chance of clinical success ($p = 0.05$). K. pneumoniae was associated with an increased chance of clinical success in comparison with the other CRGNB ($p = 0.02$). The weighted acute illness score was associated with an increased chance of clinical failure (odds ratio (OR) 2.2 for each point, $p < 0.001$). No predictors of microbiological success were identified. UTI had a lower average logarithm of hospital LOS than the other infections ($p < 0.001$). No predictors of ICU LOS were identified. Bacteremia was associated with increased treatment-related ARF compared with other sources of infection ($p = 0.01$). K. pneumoniae was associated with increased survival compared with other CRGNB ($p = 0.03$), and among infections a trend was seen for UTI ($p = 0.07$). Age (OR 1.04 per y, $p = 0.04$), Charlson score (OR 1.12 per point, $p = 0.04$), and the weighted acute illness score (OR 2.2 per point, $p < 0.001$) were associated with hospital mortality. Age (OR 10.6 per 10 y, $p = 0.01$) and Charlson score (OR 1.2 per point, $p = 0.02$) were associated with mortality at 6 months. No significant difference in outcome was observed between the different treatment regimens. Multivariate analysis showed that the weighted acute illness score was related to both clinical success (OR 0.41 per point,

Table III. Observed complications of carbapenem-resistant Gram-negative bacteria infections.

Complication	*n* (%)
Acute respiratory failure	72 (69.2)
Septic shock	59 (56.7)
Acute renal failure	55 (52.9)
Acute renal failure requiring hemodialysis	13 (12.5)
Treatment-related acute renal failure	15 (14.4)
Encephalopathy	54 (51.9)
Hyperglycemia	26 (25.0)
Acute myocardial infarction	23 (22.1)
Hyperbilirubinemia	12 (11.5)
Disseminated intravascular coagulation	4 (3.8)

$p < 0.01$) and hospital mortality (OR 2.24 per point, $p < 0.01$). Age was associated with mortality after 6 months (OR 10.5 for each 10 y, $p = 0.02$).

Discussion

For infections with CRGNB, no alternative treatment to polymyxin B or colistin is currently available. When the polymyxins were first introduced in the 1950s, requirements for approval for clinical use were much less stringent. Therefore, little is known about the PK/PD of the drugs. PK/PD studies are being done to resolve this issue and have mainly concentrated on colistin [8,23]. However, a recently published study using population PK analysis and Monte Carlo simulations concluded that doses of intravenous polymyxin B are best scaled by total body weight and the dosage selection should not be based on renal function [7].

In our institution, treatment with polymyxin B in combination with a carbapenem and rifampin has mainly been used for CRGNB infections. *In vitro* and animal data show evidence of synergy for polymyxin B with a carbapenem, as well as rifampin [9–12,14,15]. Albeit limited, clinical data support the efficacy of this regimen *in vivo* [24]. Several studies have shown an increased mortality with colistin monotherapy compared with combination therapy [14,15,25,26]. We did not observe a significant difference between different treatment regimens, which may be due to the study design and sample size. Our study was observational and lacked a control group, however it does provide further insight into the epidemiology and outcome of CRGNB infections treated with polymyxin B combination treatment.

Health care exposure was common in patients who acquired a CRGNB infection. Two-thirds of the patients had recently been admitted and half were admitted from a skilled nursing facility (SNF). Nearly three-quarters had received antibiotics in the previous 6 months. Half of the patients were ventilated at the time of infection and a third had a tracheostomy. Most patients were completely dependent in their activities of daily living. Therefore, it is not surprising that the majority of patients suffered from respiratory tract infections, UTI, and SSTI, mostly infected decubitus ulcers. Up to 89% had multiple infections during the hospitalization, which was a CRGNB in 35%. This suggests that these patients are in a cycle of recurrent infections and multiple courses of antibiotics and develop resistant organisms. The colonization rate was 55%, which is consistent with other studies, allowing for further spread of the organisms [27]. We found that patients with multiple different CRGNB infections were mainly cohorted on a separate floor. Cohorting of patients may promote further spread and transfer of resistance. This has been shown for hospitals as well as long-term care facilities [28–30]. Many of these patients were eventually discharged to a SNF. Colonization and infection occur frequently at long-term care facilities [29]. Our study shows that approximately 50% of the patients were referred from a SNF, and 18% were transferred for an active CRGNB infection. Therefore, strict infection control practices in the hospital as well as at SNFs are critical in fighting these infections. Contact precautions with gowns and gloves, and cohorting are recommended by the Centers for Disease Control and Prevention [31]. Limited data are available regarding the duration of isolation, however indefinite isolation has been suggested. Active surveillance cultures have proven useful in containing CRGNB outbreaks. However, the role for routine use is unclear. Decolonization regimens are not sufficiently effective to warrant use [31].

We observed an all-cause mortality of 47% for the hospitalization and 77% after 6 months. Nearly all mortalities were related to the underlying infection. The hospital mortality rate is similar to those in other reports [2,14,15]. Our study documents that this patient population is chronically as well as acutely ill, which is reflected by the high Charlson and APACHE IV scores. Interestingly, clinical success was more likely to occur with K. pneumoniae and UTI. K. pneumoniae was also associated with a decreased hospital mortality and a trend was seen for UTI ($p = 0.03$ and $p = 0.07$ respectively). However, this effect was not present 6 months after discharge. Treatment failure was associated with the weighted acute illness score (OR 2.2 for each point, $p < 0.001$). Age (OR 10.4 for each 10 y, $p = 0.04$), weighted acute illness score (OR 2.2 per point, $p < 0.001$), and Charlson score (OR 1.12 per point, $p = 0.04$) were associated with hospital mortality. Age (OR 10.6 per each 10 y, $p < 0.01$) and chronic illness as reflected by the Charlson score (OR 5.9 for each 5 points, $p = 0.02$) were also associated with all-cause mortality at 6 months. Less than 10% of patients with a Charlson score greater than 9 survived longer than 6 months. Further analysis did not reveal other statistically significant predictors of the measured outcomes, including gender, race, BMI, diabetes mellitus, malignancy, and chronic respiratory failure. No significant difference in outcome was seen for the different treatment regimens, which could be due to the sample size. Further studies evaluating combination treatment especially with sulbactam and tigecycline are needed.

Polymyxin B and colistin use fell out of favor in the 1970s due to the availability of safer and more efficacious drugs. The main adverse events are neph-

rotoxicity and neurotoxicity. Treatment-related renal failure occurred in 14.4% in our study and was mostly reversible. No patients needed hemodialysis for treatment-related renal failure. Rates between 4% and 55% of renal injury due to polymyxin B have been reported [32]. The incidence of nephrotoxicity seems to be lower with polymyxin B than with colistin [33]. The source of infection was the only predictor of treatment-related renal failure. Renal failure occurred more often with bacteremia ($p = 0.01$). However, this was based on only 5 subjects with isolated bacteremia. This effect disappeared when all patients with bacteremia ($n = 17$) were included ($p = 0.06$). Due to the severity of illness and debilitating co-morbidities we were not able to evaluate neurotoxicity.

Polymyxins B and E are bactericidal agents that act on LPS on the bacterial cell wall and on the outer membrane, with a detergent action. Their effects are concentration-dependent and no post-antibiotic effect is seen. Prolonged antibiotic infusions are not beneficial as shown in a small study of 27 patients evaluating continuous infusion of polymyxin B [34]. Recent PK/PD studies with colistin suggest that the average drug concentrations achieved with currently recommended interval dosing are marginally therapeutic for sensitive strains. Higher doses are more effective but are associated with a substantially increased toxicity [23,35]. With current dosing, the occurrence of resistance is likely to occur with monotherapy, which could explain the increased mortality compared with combination therapy [36]. A recently published study suggested that polymyxin B dosing should not be adjusted for renal function as it is only minimally cleared renally. Dosing should be based on total body weight [24]. This may possibly explain the observed treatment failure in patients with renal insufficiency, which may in fact be due to underdosing [37]. Polymyxin-resistant strains are reported more frequently [3,7]. Other than novel, less toxic polymyxin derivatives, a new aminoglycoside (ACHN-490), and a new beta-lactamase inhibitor (NXL104), no drugs are in late-stage development [38,39]. Strategies for the treatment of polymyxin-resistant strains are combination treatment with a polymyxin, a carbapenem, and/or rifampin. *In vitro* animal, and limited clinical data show synergy also for these strains [23,35,36]. Our study did not show a significant benefit for added rifampin. However, this may be due to methodological reasons.

Our study has several major limitations, including the unblinded and observational design, lacking a control group. The research group was notified of new subjects by the pharmacy, hence patients with CRGNB infections who were not treated with polymyxin B were not included. Patients were not empirically treated with polymyxin B, causing a delay in effective treatment, and dosing was adjusted for renal function, which may have affected the outcome. Polymyxin B sensitivities were not performed on clinical specimens, as breakpoints are not available. However, a survey previously performed in our hospital determined a greater than 90% 'sensitivity' of CRGNB based on drug concentrations achieved with routine dosing (unpublished data). The score for acute illness that we used is not validated. The decision to use additional rifampin was made by the primary infectious diseases specialist, which may have introduced bias. Microbiological success was determined by clearance of follow-up cultures, which were not routinely performed, and this may have introduced bias. No data regarding the mechanism of resistance for the organisms was available, making it impossible to determine the optimal treatment for the specific organism and its specific resistance mechanism. Despite these limitations, our study is the largest single-center study evaluating a range of CRGNB infections treated with polymyxin B combination therapy. Further studies concentrating on the pharmacokinetics, pharmacodynamics, susceptibility breakpoints, and side effect profile, especially for combination treatments including tigecycline, sulbactam, and rifampin, are needed.

In conclusion, CRGNB infections are strongly associated with previous antibiotic and health care exposure. Increased clinical success was observed with UTI and infections with K. pneumoniae. Clinical failure was associated with the severity of the acute illness. The observed hospital mortality was 47%, which increased to 77% at 6 months. Mortality was related to age, severity of the acute illness, and Charlson score. No significant difference in outcome was noted between the different combination treatment regimens.

Declaration of interest: No conflict of interest to declare.

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