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Effectiveness and safety of colistin: prospective comparative cohort study

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Background: Colistin has re-entered clinical use by necessity. We aimed to assess its effectiveness and safety compared with newer antibiotics.

Methods: This was a single-centre, prospective cohort study. Inclusion criteria were microbiologically documented pneumonia, urinary tract infection, surgical site infection, meningitis or bacteraemia treated appropriately with colistin versus imipenem, meropenem or ampicillin/sulbactam (comparators). All consecutive patients were included, only once, between May 2006 and July 2009. The primary outcome was 30 day mortality. Multivariable and Cox regression survival analyses were used to adjust comparisons between groups. Odds ratios (ORs) or hazard ratios (HRs) with 95% confidence intervals are reported.

Results: Two hundred patients treated with colistin and 295 patients treated with comparators were included. Treatment with colistin was associated with older age, admission from healthcare facilities, mechanical ventilation and lower rate of early appropriate antibiotic treatment. The 30 day mortality was 39% (78/200) for colistin versus 28.8% (85/295) for comparators; unadjusted OR 1.58 (1.08–2.31). In the adjusted analysis the OR was 1.44 (0.91–2.26) overall and 1.99 (1.06–3.77) for bacteraemic patients ($n=220$). At the end of follow-up, treatment with colistin was significantly associated with cumulative mortality; adjusted HR 1.27 (1.01–1.60) overall and 1.65 (1.18–2.31) among patients with bacteraemia. Nephrotoxicity at the end of treatment was more frequent with colistin; OR adjusted for other risk factors for nephrotoxicity 3.31 (1.54–7.08). Treatment with colistin was followed by increased incidence of *Proteus* spp. infections during a 3 month follow-up.

Conclusions: The need for colistin treatment is associated with poorer survival. Adjusted analyses suggest that colistin is less effective and more toxic than β-lactam antibiotics.

Keywords: polymyxin, multidrug-resistant Gram-negative bacteria, *Klebsiella*, *Acinetobacter*, hospital-acquired infections

Introduction

The emergence of multidrug-resistant Gram-negative bacteria in hospitals has led to renewed interest in older drugs. Foremost among these is the polymyxin class of antibiotics that have been abandoned for many years following reports of unacceptable toxicity.[1] Lacking an evidence base on their comparative efficacy relative to currently used antibiotics, their role in the empirical and definitive treatment of patients remains unclear.

Colistin is the main polymyxin that recently re-entered clinical use by necessity.[2] Several contemporary studies report an acceptable efficacy and safety profile of colistin in the treatment of severe infections caused by multiresistant Gram-negative bacteria.[3–10] However, only a few studies were comparative and these lacked the sample size needed to compare colistin versus state-of-the-art antibiotics and to adjust for the expected different characteristics of patients infected by bacteria susceptible only to colistin.[11–14]

A randomized controlled trial comparing colistin with modern antibiotics would entail prescribing colistin to patients with infections caused by bacteria susceptible to other antibiotics and would be unethical. We performed a prospective observational

study comparing colistin with β-lactam antibiotics used for similar types of infections.

Methods

Design

This was a prospective cohort study. Data collection and analysis were prospectively planned. The study was approved by the local ethics committee. Informed consent was waived given that no intervention was planned and collected data were stored anonymously.

Setting

The study was carried out in the Rabin Medical Center, Beilinson Hospital, a 900 bed primary and tertiary care hospital with 32 intensive care unit (ICU) beds in three units (mixed medical/surgical, neurosurgical and thoracic-surgical) and an active solid organ transplantation programme.

Participants

We included patients fulfilling the CDC definitions for nosocomial infections:[15] pneumonia; ventilator-associated pneumonia (VAP); urinary tract infection; deep or organ-space surgical site infection; neurosurgical meningitis; and bacteraemia of any source. Only infections caused by Gram-negative bacteria susceptible to colistin, imipenem, meropenem or ampicillin/sulbactam and treated with one of these antibiotics were included. Thus, only appropriately treated, microbiologically documented, infections were considered. Patients were identified through the hospital's pharmacy registry of restricted antibiotics. All consecutive patients fulfilling diagnostic criteria during the study period were included.

As a policy in our hospital, colistin was reserved for treatment of bacteria resistant to carbapenems and other antibiotics (except aminoglycosides). Ampicillin/sulbactam was used for the treatment of multidrug-resistant *Acinetobacter baumannii* and the carbapenems were reserved for treatment of extended-spectrum β-lactam-producing and other Gram-negative bacteria resistant to narrower-spectrum antibiotics.[16] All antibiotic choices were made by the treating physicians in consultation with infectious disease experts, since use of the study antibiotics mandated approval.

Exposure

The exposure variable of interest was treatment with colistin versus the other study antibiotics (hence 'comparators'). The preparation used was colistin sulphomethate sodium and the locally recommended daily dose for patients with normal renal function was 6–9 MU (million units) in three divided doses (equivalent to 480–720 mg of colistimethate sodium or 180–270 mg of colistin base activity). Patients on haemodialysis or haemofiltration received 1–2 MU twice daily.

Variables

Given the non-random design of the study, detailed data collection was planned to capture the differences between patients treated with colistin and those treated with comparators. Data were prospectively collected from the onset of infection (the date the culture was obtained) until 30 days, unless otherwise specified. We collected data on: demographics; background conditions including functional capacity before admissions and the Charlson and McCabe scores; place of infection acquisition; hospitalization duration, antibiotics, blood products, surgical or other procedures, dialysis, immune suppression and trauma in the 30 days prior to infection onset; catheters, devices, ventilatory, renal and haemodynamic support at the time of infection onset; and infection severity as reflected by septic shock, new need for haemodynamic support, haematology and chemistry profile, and the sequential organ failure assessment (SOFA) score. We collected data on empirical antibiotic treatment for the index infection and its appropriateness, dosing of study antibiotics, duration of treatment and all concomitant and subsequent antibiotics. Bacteria causing the index infection, as well as all clinical isolates identified during a 3 month follow-up, and their antibiotic susceptibilities were recorded. Cultures and other blood samples were taken as clinically indicated.

Outcomes

The primary outcome was all-cause mortality 30 days after start of treatment. Secondary outcomes included: survival until November 2009; development of septic shock; fever duration for the index infection; secondary infections within 30 days; development of resistance; adverse events, mainly renal failure, diarrhoea and *Clostridium difficile*-associated diarrhoea; and duration of hospital stay. Secondary infections were defined as a new focus of infection, associated with clinical signs or symptoms, caused by different bacteria or susceptibility phenotypes. Development of resistance was defined as clinical infection caused by a pathogen resistant to the study antibiotics appearing >5 days after start of the antibiotic and within 1 or 3 months.

Creatinine and urea values were recorded before infection onset and thereafter once weekly for 4 weeks. Renal failure was defined per protocol. For patients with baseline creatinine <1.2 mg/dL this was: creatinine ≥2 mg/dL; ≥50% reduction from baseline glomerular filtration rate (GFR); or new need for renal replacement therapy. For patients with baseline creatinine ≥1.2 mg/dL this was: ≥50% increase in creatinine; ≥50% reduction from baseline GFR; or new need for renal replacement therapy. GFR was estimated using the Modification of Diet in Renal Disease Study [$eGFR = 175 \times \text{standardized Scr}^{-1.154} \times \text{age}^{-0.203} \times 0.742$ (if female); where Scr stands for serum creatinine].[17] All other clinical adverse events were recorded; no specific evaluation was conducted to detect neurotoxicity.

Sample size

We estimated a 1:2 colistin versus comparator treatment rate of inclusion. A sample of 390 patients was planned to detect an odds ratio (OR) of ≥1.6 in favour of comparators (power 0.7, alpha = 0.05), assuming a 40% mortality rate with comparators. An OR of 1.6 was selected based on the difference observed between patients receiving appropriate versus inappropriate antibiotic treatment.[18] Data collection was subsequently extended to increase power. The final sample had a power of 0.75 and 0.99 to detect significant differences in the observed 30 day and end of follow-up mortality, respectively (two-sided alpha = 0.05).

Data sources

Data were collected through patient chart review and computerized medical records. The electronic patient system used in our hospital links data on previous hospitalizations, care in primary care clinics, chronic medications and death data from the national population registry. Isolates were identified using routine microbiological methods; susceptibility to colistin was tested using disc diffusion applying the ≥11 mm cut-off of susceptible, for all isolates.[2,19]

Statistical analysis

Dichotomous data were compared using a χ^2 test. Normally distributed continuous data are expressed as means with standard deviations and were compared using the *t*-test. Otherwise, values are presented as medians with ranges and were compared using the Mann–Whitney

U-test. Kaplan–Meier survival analysis was conducted and treatment groups were compared using the log rank test. Expecting *a priori* differences between patients treated with colistin and those treated with comparators, we adjusted for confounding by using multivariable analysis, to produce a risk-adjusted treatment effect. We conducted binary backward logistic regression analysis for 30 day mortality and Cox backward regression survival analysis. ORs or hazard ratios (HRs) are reported, respectively, with 95% confidence intervals (CIs). Since the data set was extensive, we selected for inclusion in the model variables associated with the outcome at the 0.01 significance level on univariate analysis to avoid overfitting, and omitted individual variables comprising the prognostic scores included in the model (e.g. Charlson and SOFA scores). Treatment arm was forced into both models. Missing values for laboratory measures used in the multivariable analysis were replaced using the series mean (maximum 12 patients for albumin). Variables that did not significantly contribute to the multivariable model were removed stepwise and all variables remaining in the final model are presented. In a secondary analysis, we forced the propensity for treatment with colistin into the multivariable analysis. The propensity score comprised the probability for treatment with colistin derived from a binary regression analysis with colistin treatment as the dependent variable and all baseline characteristics differing between the study groups as covariates. Analyses were conducted using PASW statistics 17.0 (SPSS Inc.).

Results

Between May 2006 and July 2009, 495 consecutive patients with a first infectious episode fulfilled the inclusion criteria and were included. Two hundred patients were treated with colistin and 295 with comparator antibiotics, consisting of imipenem (111), meropenem (54) and ampicillin/sulbactam (130) (Table 1). The study cohort comprised patients mostly admitted from home (72%) and previously independent in their functional status (62%). Half of the patients underwent an operation within 30 days of infection onset and 18% had solid organ transplantation. Cancer, mainly haematological, was rare. All infections were healthcare associated, 92.7% were acquired in the hospital and 86.7% of patients had received antibiotic treatment in the 30 days prior to the index infection. Invasive procedures and devices were highly prevalent. Twenty percent of patients were in an ICU at onset of infection.

Patients treated with colistin had several poorer prognostic features as compared with those treated with comparators, being older, more frequently admitted from nursing homes or other healthcare facilities and more frequently mechanically ventilated at infection onset. Albumin levels were significantly lower in the colistin group. Several other features did not reach statistical significance, but indicated that patients given colistin were different from those treated with comparators, including more infections acquired in the ICU and a lower rate of appropriate antibiotic treatment on the day of infection onset. *Klebsiella pneumoniae* infections were more common among colistin-treated patients, due to the spread of carbapenem-resistant *K. pneumoniae* in Israel during the study period, while *A. baumannii* and other Gram-negative bacteria were more frequently treated with imipenem, meropenem or ampicillin/sulbactam. The median treatment duration was 10 days and was similar for colistin and comparators; more patients with colistin were treated for <72 h, mainly due to early death. The mean dose of colistin among patients with a normal GFR was 6.1 ± 2.3 MU/day (mean 7.8 MU/day per 100 mL/min GFR).

All-cause mortality

The 30 day mortality rate was 39% (78/200) versus 28.8% (85/295) for colistin versus comparators ($P=0.018$). The difference between the treatment groups was statistically significant in the subgroups of patients with infections caused by *K. pneumoniae* and among those that did not receive the alternative study antibiotic during the 30 days following the index infection (Table 2). Other risk factors for mortality are listed in Table S1 [available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/)]. Risk factors retained in the final model as significantly and independently associated with 30 day mortality included age, functional capacity, McCabe score, bacteraemia and sepsis severity as reflected by the SOFA score (Table 3). The association of colistin with 30 day mortality did not reach statistical significance; OR 1.44 (95% CI 0.91–2.26). Including the propensity score in the final model resulted in a similar OR of 1.48 (95% CI 0.92–2.39). Among patients not given the alternative treatment arm in the 30 day follow-up, the adjusted OR was 1.67 (95% CI 0.97–2.87). In the subgroup of patients with bacteraemia, treatment with colistin was significantly associated with 30 day mortality; adjusted OR 1.99 (95% CI 1.06–3.77).

At the time of data analysis, 67% (134/200) of patients treated with colistin and 53.9% (159/295) of patients treated with comparators died [median follow-up 747 days (range 82–1272) for those alive and 27 days (1–1016) for those who died]. The median survival was 72 days with colistin versus 245 with comparators (log rank $P=0.001$) (Figure 1). The risk for death at end of follow-up was mediated mainly by variables related to the index infection (Table 4). Treatment with colistin was significantly associated with death [overall adjusted HR 1.27, 95% CI 1.01–1.60; propensity-adjusted HR 1.34 (95% CI 1.05–1.72)] in the subgroup of patients with bacteraemia [1.65 (95% CI 1.18–2.31)] and in the subgroup of patients without treatment overlap [1.45 (95% CI 1.10–1.89)].

Secondary outcomes

Patients treated with colistin had a significantly higher rate of septic shock as a complication of their infection and experienced longer durations of fever, more secondary infections and longer hospital stay (Table 5). The occurrences of diarrhoea, *C. difficile*-associated diarrhoea and neuropathy were not significantly different.

Renal failure occurred more frequently among patients treated with colistin. Results were unchanged when excluding patients treated concomitantly with aminoglycosides. An adjusted analysis was conducted for renal failure at week 2 (mean end of treatment) for patients alive at 2 weeks ($n=379$). Independent risk factors for renal failure included vasopressor treatment (OR 10.83, 95% CI 4.86–24.12), colistin treatment (OR 3.31, 95% CI 1.54–7.08), chronic pulmonary disease and lower sodium levels at infection onset. Renal failure mandating haemodialysis was rare and not significantly different. No correlation was observed between daily or cumulative colistin doses and nephrotoxicity (data not shown).

Development of resistance was assessed by monitoring of clinical isolates identified during a 3 month follow-up. Isolation of the same type of bacteria as the index infection with a

Table 1. Patient characteristics for colistin and comparators[a]

	Colistin, $n=200$	Comparators, $n=295$	P value
Demographics			
Age (years), mean ± SD	64.7 ± 18.2	61.2 ± 18.8	0.037[b]
Female	77 (38.5)	116 (39.3)	0.854
Admission from home	133 (66.5)	223 (75.6)	0.027[b]
Hospital ward at infection onset			0.208
intensive care unit	47 (23.5)	52 (17.6)	
medical wards	74 (37)	108 (36.6)	
surgical wards	79 (39.5)	135 (45.8)	
Duration of hospitalization before infection (days), median (range)	11 (0–68)	11 (0–116)	0.271
Background conditions			
Admission diagnosis			0.952
infectious	62 (31)	88 (29.8)	
medical	51 (25.5)	66 (22.4)	
emergency surgery	27 (13.5)	44 (14.9)	
elective surgery	22 (11)	38 (12.9)	
solid organ transplantation	17 (8.5)	26 (8.8)	
trauma	21 (10.5)	33 (11.2)	
Functional capacity before admission			0.181
independent	122 (61)	185 (62.7)	
needs help for daily activities	21 (10.5)	44 (14.9)	
dependent	22 (11)	32 (10.8)	
bedridden	35 (17.5)	34 (11.5)	
McCabe score			0.181
no fatal disease	112 (56)	156 (52.9)	
ultimately fatal disease	55 (27.5)	102 (34.6)	
rapidly fatal disease	33 (16.5)	37 (12.5)	
Immune suppression			
any	48 (24)	84 (28.5)	0.269
solid cancer	23 (11.5)	41 (13.9)	0.435
haematological cancer	9 (4.5)	17 (5.8)	0.537
solid organ transplantation	33 (16.5)	54 (18.3)	0.605
Congestive heart failure	49 (24.5)	68 (23.1)	0.710
Diabetes mellitus	64 (32)	85 (28.8)	0.448
Chronic pulmonary disease	48 (24)	68 (23.1)	0.807
Chronic renal failure (creatinine >3 mg/dL)	16 (8)	23 (7.8)	0.934
Charlson score, median (range)	2 (0–11)	2 (0–11)	0.629
Devices/status at onset of infection			
Mechanical ventilation	124 (62)	150 (50.8)	0.014[b]
Urinary catheter	155 (77.5)	203 (68.8)	0.034[b]
Central venous catheter	84 (42)	120 (40.7)	0.769
Arterial monitoring	59 (29.5)	72 (24.4)	0.207
Surgery within 30 days	100 (50)	149 (50.5)	0.912

Continued

Table 1. *Continued*

	Colistin, $n=200$	Comparators, $n=295$	P value
Infection characteristics			
Bacteraemia	92 (46)	128 (43.4)	0.566
Source of infection			0.110
ventilator-associated pneumonia	61 (30.5)	82 (27.8)	
other hospital-acquired pneumonia	37 (18.5)	48 (16.3)	
surgical site infection	22 (11)	45 (15.3)	
urinary tract infection	21 (10.5)	24 (8.1)	
neurosurgical-related meningitis	1 (0.5)	14 (4.7)	
others	21 (10.5)	33 (11.2)	
primary bacteraemia	37 (18.5)	49 (16.6)	
Septic shock at onset	22 (11)	29 (9.8)	0.674
Acute renal failure at onset, *n*/*N* (%)	25/200 (12.5)	28/293 (9.6)	0.300
Pathogen causing infection			
Acinetobacter baumannii	107 (53.5)	178 (60.3)	0.131
Klebsiella pneumoniae	104 (52)	80 (27.1)	<0.001[b]
Pseudomonas aeruginosa	31 (15.5)	52 (17.6)	0.534
other Gram-negative bacteria	43 (21.5)	98 (33.2)	0.005
polymicrobial infection	70 (35)	106 (35.9)	0.832
Albumin (g/dL), mean ± SD	$n=197$, 2.34 ± 0.60	$n=286$, 2.54 ± 0.68	0.001[b]
White blood cells ($\times10^3/\mu$L), median (range)	$n=199$, 13.1 (0.4–58.3)	$n=293$, 12.8 (0.1–77.1)	0.039[b]
Haematocrit (%), mean ± SD	$n=199$, 29.6 ± 4.8	$n=293$, 29.7 ± 5	0.753
Creatinine (mg/dL), median (range)	$n=200$, 1.1 (0.1–9.1)	$n=293$, 1.0 (0.1–8.8)	0.094
SOFA score, median (range)	4 (0–18)	4 (0–19)	0.833
Treatment			
Appropriate treatment on day of infection presentation, *n*/*N* (%)	14/198 (7.1)	36/290 (12.4)	0.056
Appropriate treatment at 24 h, *n*/*N* (%)	45/198 (22.7)	61/290 (21)	0.656
Time to appropriate treatment (days), median (range)	$n=195$, 3 (0–20)	$n=286$, 3 (0–22)	0.611
Index treatment duration (days), median (range)	$n=197$, 10 (1–42)	$n=291$, 11 (1–30)	0.493
Index treatment for <72 h	28 (14)	14 (4.7)	<0.001
Receipt of alternative antibiotic after index infection[c]	42 (21)	66 (22.4)	0.655
Treatment with aminoglycosides	23 (11.5)	18 (6.1)	0.032

[a]Data are reported on all patients, unless indicated otherwise. The number of patients (%) is shown, unless indicated otherwise. All laboratory values are reported at onset of infection. Values distributed normally are reported as means ± SD and were analysed using the *t*-test; others are reported as medians with ranges and were analysed using the Mann–Whitney test.
[b]Variable used to construct the propensity score for treatment with colistin.
[c]Patients in the colistin arm treated with one of the comparator drugs and patients in the comparator arm treated with colistin in a 30 day follow-up after the index infection.

resistance phenotype to the study intervention (initially susceptible to the intervention) occurred more frequently in the comparator arm ($P=0.005$). Any Gram-negative bacteria resistant to colistin were isolated more frequently among patients treated with colistin after 3 months, but not after 1 month. These were mostly *Proteus* and *Serratia* spp. that are inherently resistant to colistin; other bacteria developing resistance to colistin (*K. pneumoniae*, *Pseudomonas aeruginosa* and *Stenotrophomonas maltophilia*) were observed in 5/158 (3.2%) patients treated with colistin versus 6/229 (2.6%) patients treated with comparators. The comparison of Gram-negative bacteria resistant to comparator antibiotics was meaningless, since all patients treated with colistin had started with an infection caused by bacteria resistant to comparator antibiotics.

Discussion

Attesting to the fact that colistin was reserved for treatment of infections caused by bacteria resistant to all other antibiotics, patients treated with colistin were at higher risk for adverse outcomes than patients treated with β-lactams. They were older, more frequently admitted from healthcare facilities and more frequently mechanically ventilated when acquiring the infection. The unadjusted odds for 30 day mortality were 60% higher among colistin-treated patients. The adjusted analysis showed higher mortality in the colistin group that was statistically significant in the subgroup of patients with bacteraemia. At the end of follow-up, cumulative mortality remained significantly higher with colistin when adjusted for other risk factors for survival, with HRs ranging between 1.3

Table 2. Unadjusted 30 day mortality, *n* (%)

	Colistin, *n*=200	Comparators, *n*=295	Unadjusted OR (95% CI)
All patients	78 (39)	85 (28.8)	1.58 (1.08–2.31)
Bacteraemia	45/92 (48.9)	47/128 (36.7)	1.65 (0.96–2.84)
No overlap	66/158 (41.8)	62/229 (27.1)	1.93 (1.26–2.97)
Main pathogen group			
Acinetobacter baumannii	39/107 (36.4)	53/178 (29.8)	1.35 (0.81–2.25)
Klebsiella pneumoniae	40/104 (38.5)	18/80 (22.5)	2.15 (1.12–4.15)

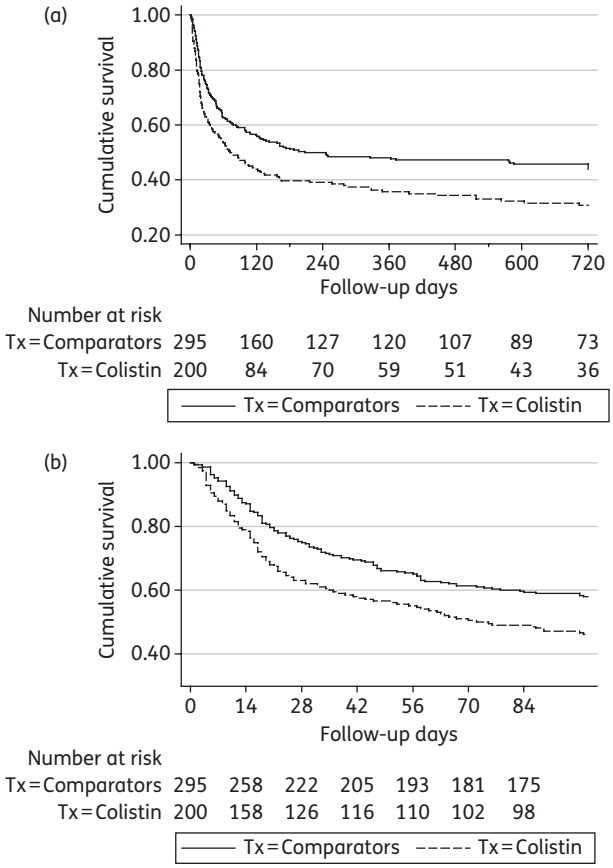

Figure 1. Kaplan–Meier survival analysis, by study arm. (a) Two years of follow-up. (b) Three months of follow-up.

Table 3. Adjusted analysis for 30 day mortality

	OR (95% CI)[a]	
Risk factor	all patients, *n*=495	bacteraemia, *n*=220
Colistin arm of the study	1.44 (0.91–2.26), *P*=0.116	1.99 (1.06–3.77), *P*=0.033
Age[b]	1.04 (1.03–1.06), *P*<0.001	1.04 (1.02–1.07), *P*<0.001
McCabe score		not significant
no fatal disease	0.42 (0.23–0.79), *P*=0.007	
ultimately fatal disease	0.52 (0.27–1.00), *P*=0.051	
rapidly fatal disease	reference	
Independent functional capacity on admission	0.51 (0.31–0.84), *P*=0.008	0.44 (0.22–0.88), *P*=0.021
Bacteraemia	1.95 (1.25–3.05), *P*=0.003	not relevant
SOFA score at onset of infection[b]	1.28 (1.18–1.38), *P*<0.001	1.32 (1.19–1.47), *P*<0.001
Albumin at onset of infection[b]	0.65 (0.42–1.01), *P*=0.057	not significant

[a]Binary backward logistic regression analysis was performed, forcing treatment arm into the final model, Hosmer and Lemeshow goodness of fit χ^2 6.775, df 8, *P*=0.561 (all patients), area under the receiver operating characteristic (ROC) curve 0.81, 95% CI 0.77–0.85. Variables included in the model and not retained in the final model included: trauma as the admission diagnosis; Charlson score; presence of nasogastric tube; urinary catheter and mechanical ventilation at infection onset; and those listed as not significant in the table.
[b]Continuous variable, increment of 1 year (age), 1 point (SOFA) and 1 g/dL (albumin).

Table 4. Adjusted survival analysis

Risk factor	HR (95% CI)[a]	
	all patients, $n=495$	bacteraemia, $n=220$
Colistin arm of the study	1.27 (1.01–1.60), $P=0.049$	1.65 (1.18–2.31), $P=0.004$
Age[b]	1.03 (1.02–1.04), $P<0.001$	1.02 (1.01–1.04), $P<0.001$
McCabe score		not significant
no fatal disease	0.53 (0.38–0.73), $P<0.001$	
ultimately fatal disease	0.65 (0.47–0.90), $P=0.001$	
rapidly fatal disease	reference	
Independent functional capacity on admission	0.80 (0.62–1.05), $P=0.104$	not significant
Hospitalization in medical ward at onset of infection	1.56 (1.19–2.05), $P=0.001$	2.37 (1.61–3.50), $P<0.001$
Mechanical ventilation at onset of infection	not significant	1.44 (0.95–2.18), $P=0.085$
Bacteraemia	1.37 (1.08–1.73), $P=0.008$	not relevant
SOFA score at onset of infection[b]	1.13 (1.09–1.18), $P<0.001$	1.12 (1.05–1.18), $P<0.001$
Albumin at onset of infection[b]	0.79 (0.62–0.99), $P=0.049$	not significant

[a]Cox backward regression survival analysis, forcing treatment arm into the final model, likelihood ratio test χ^2 206.0, df 9, $P<0.001$ for all patients. Variables included in the model and not retained in the final model included: trauma as the admission diagnosis; urinary tract infection or surgical site infection as the source of the index infection; presence of nasogastric tube; urinary catheter at infection onset; and those listed as not significant in the table.
[b]Continuous variable, increment of 1 year (age), 1 point (SOFA) and 1 g/dL (albumin).

and 1.6 among all patients, those with bacteraemia and those that received only the antibiotic to which they were assigned. Nephrotoxicity at end of treatment was significantly more frequent among patients treated with colistin, with an adjusted OR >3. These results are compatible with the hypothesis that colistin is less effective and more toxic than β-lactam antibiotics.

Previous comparative studies have reported similar outcomes for colistin versus carbapenems or ampicillin/sulbactam. Reina *et al.*[14] prospectively compared colistin (55 patients) and imipenem (130 patients) in an ICU setting. Patients given colistin had higher APACHE (Acute Physiology and Chronic Health Evaluation) scores and none had received appropriate empirical antibiotic treatment, yet similar outcomes were observed. Compared with our study, this cohort included younger patients (mean 63 versus 41 years), with fewer co-morbidities (78% versus 54% with no fatal underlying disease) and lower in-hospital mortality (39% versus 28%), respectively. Kallel *et al.*[13] matched age, SAPS II (Simplified Acute Physiology Score II) and PaO_2/FiO_2 in a retrospective parallel cohort study comparing colistin (60 patients) with imipenem (60 patients) for VAP. Mortality and infection resolution were not significantly different and no renal toxicity was observed, but there may have been other differences between the patient groups that could not be captured in a retrospective design. A small trial compared colistin with ampicillin/sulbactam for VAP, but the method of quasi-randomization (alternation) permitted differential accrual into the trial and the sample size (28 patients) was insufficient for outcome assessment.[11] A rate of nephrotoxicity similar to ours was observed in a cohort of 66 patients treated with colistin.[20] In this study 17% of young soldiers with few co-morbidities developed renal injury (the category matching our definition of nephrotoxicity) using the RIFLE criteria,[21] 1 week after end of therapy.

While previous studies addressed infections caused by *Acinetobacter* and *Pseudomonas* spp., many patients in our study were infected by multidrug-resistant *K. pneumoniae* where the difference between colistin and comparators was most marked. We included all consecutive patients that were treated with colistin and comparators for defined infections, to reduce the risk of biased inclusion. Two features unique to our study were the assessment of long-term survival and the subgroup analysis of patients that did not crossover to the alternative treatment arm for subsequent infections. These analyses underlined the disadvantage of colistin. The ominous long-term survival of patients included in our cohort is remarkable. Most patients were admitted from home with full functional capacity; many were admitted for trauma, solid organ transplantations or other surgery. These results highlight the survival cost of resistant infections in hospital.

The main limitation of our study is the lack of randomization. It is possible that no method can completely adjust for the differences between patients infected with pan-resistant bacteria and those infected by more susceptible bacteria. Despite adherence to CDC criteria for diagnosis of clinically relevant infections, some patients with non-clinical isolates may have been included. However, this occurrence should not have introduced bias in the comparisons. The average colistin dose used was 6 MU/day, equivalent to 180 mg of colistin base activity, but optimal dosing among critically ill patients is unknown.[20]

We observed a higher rate of phenotype change from susceptible to resistant among patients treated with carbapenems than

Table 5. Secondary outcomes

	Colistin	Comparators	*P* value
Fever duration (days), median (25th–75th percentile)[a]	*n*=102, 3 (0–7)	*n*=192, 2 (0–4)	0.025
Development of septic shock, *n*/*N* (%)	71/200 (35.5)	62/295 (21)	<0.001
Diarrhoea, within 30 days, *n*/*N* (%)	25/195 (12.8)	50/291 (17.2)	0.192
Clostridium difficile-associated diarrhoea, *n*/*N* (%)	5/196 (2.6)	11/292 (3.8)	0.460
Neuropathy, *n*/*N*	0/195	4/292	0.101
Seizures, *n*/*N*	2/196	1/292	0.348
Haemorrhage (major), *n*/*N*	2/195	10/292	0.094
Renal failure[b], *n*/*N* (%)			
week 1	26/168 (15.5)	17/244 (7)	0.006
week 2	23/152 (15.1)	15/227 (6.6)	0.007
week 4	13/128 (10.2)	10/198 (5.1)	0.079
new need for haemodialysis after onset	12/200 (6)	15/295 (5.1)	0.660
Secondary infection within 30 days, *n*/*N* (%)	72/195 (36.9)	83/292 (28.4)	0.049
Development of resistance[c], *n*/*N* (%)			
index bacteria, resistance to study drug at 3 months	16/158 (10.1)	48/229 (21)	0.005
any Gram-negative resistant to colistin at 1 month	25/158 (15.8)	26/229 (11.4)	0.201
any Gram-negative resistant to colistin at 3 months	42/158 (26.6)	36/229 (15.7)	0.009
Proteus spp. at 3 months	35/158 (22.2)	29/229 (12.7)	0.014
Hospital stay post-infection (days), median (25th–75th percentile)[a]	*n*=107, 26 (17–40)	*n*=196, 21 (13–35)	0.021

[a]Duration was measured in days from onset of infection, among patients discharged alive.
[b]Weeks refer to time from infection onset. The denominator refers to the number of patients alive at the indicated time, with available renal function assessment. Need for haemodialysis was defined between infection onset and 30 days for patients that were not on dialysis prior to infection.
[c]Development of resistance among clinical isolates at the timepoint specified. All comparisons were restricted to patients that did not receive the alternative antibiotic during the 30 day period. *Proteus* spp. include the genera *Proteus*, *Morganella* and *Providencia*, which are inherently resistant to colistin.

among those treated with colistin. This occurred in an environment where carbapenem resistance was prevalent, and we did not perform molecular studies to prove development of resistance. In a 3 month follow-up, the use of colistin was associated with a higher rate of appearance of *Proteus* spp., which are inherently resistant to colistin. Throughout the study period we observed few other colistin-resistant bacteria. We started the study as soon as systemic colistin was re-introduced to our hospital's formulary. With longer use, a stronger shift towards bacteria resistant to colistin may occur as development of colistin resistance has been observed.[22–24]

Further research should attempt to devise methods to improve outcomes with colistin. Determination of MICs for isolates using Etest is preferable to using disc diffusion.[19] A recent pharmacokinetic study suggested using loading doses in critically ill patients, since colistin plasma concentrations were insufficient before steady state.[25] Combination with rifampicin has been suggested.[26] Well-conducted studies reporting on outcomes of colistin versus aminoglycosides or their combination might improve our understanding.

Following this study, we believe that the use of colistin should be reserved only for treatment of infections that are resistant to other, more potent antibiotics. New antibiotics to combat multidrug-resistant Gram-negative infections are urgently needed.[27] The dismal survival demonstrated in our cohort of inpatients shows the cost of antibiotic resistance in hospitals. Resistance to carbapenems was associated with a median survival of 72 days. First and foremost, care must be taken to avoid the emergence and spread of bacteria for which we have no effective treatment.

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Transparency declarations

All authors declare no conflicts of interest.

Author contributions

Planned the study: J. B.; L. L.; and M. P. Collected data: M. C.; E. G.; P. L.; S. L.; A. L., M. P.; M. R.; and D. Y. Data analysis: L. L.; and M. P. Wrote the manuscript: M. P. Review and approval of the final manuscript: all authors.

Supplementary data

Table S1 is available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/).

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