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Systematic review

Systematic review on estimated rates of nephrotoxicity and neurotoxicity in patients treated with polymyxins

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ABSTRACT

Background: Nephrotoxicity and neurotoxicity are commonly associated with polymyxin treatment; however, the emergence of multidrug-resistant Gram-negative bacteria with limited therapeutic options has resulted in increased use of polymyxins.
Objectives: To determine the rates of nephrotoxicity and neurotoxicity during polymyxin treatment and whether any factors influence these.
Data sources: Medline, Embase and Cochrane Library databases were searched on 2 January 2020.
Study eligibility criteria: Studies reporting nephrotoxicity and/or neurotoxicity rates in patients with infections treated with polymyxins were included. Reviews, meta-analyses and reports not in English were excluded.
Participants: Patients hospitalized with infections treated with systemic or inhaled polymyxins were included. For comparative analyses, patients treated with non–polymyxin-based regimens were also included.
Methods: Meta-analyses were performed using a random-effects model; subgroup meta-analyses were conducted where data permitted using a mixed-effects model.
Results: In total, 237 reports of randomized controlled trials, cohort and case–control studies were eligible for inclusion; most were single-arm observational studies. Nephrotoxic events in 35,569 patients receiving polymyxins were analysed. Overall nephrotoxicity rate was 0.282 (95% confidence interval (CI) 0.259–0.307). When excluding studies where >50% of patients received inhaled-only polymyxin treatment or nephrotoxicity assessment was by methods other than internationally recognized criteria (RIFLE, KDIGO or AKIN), the nephrotoxicity rate was 0.391 (95% CI 0.364–0.419). The odds of nephrotoxicity were greater with polymyxin therapies compared to non–polymyxin-based regimens (odds ratio 2.23 (95% CI 1.58–3.15); $p < 0.001$). Meta-analyses showed a significant effect of polymyxin type, dose, patient age, number of concomitant nephrotoxins and use of diuretics, glycopeptides or vasopressors on the rate of nephrotoxicity. Polymyxin therapies were not associated with a significantly different rate of neurotoxicity than non–polymyxin-based regimens (p 0.051). The overall rate of neurotoxicity during polymyxin therapy was 0.030 (95% CI 0.020–0.043).

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Conclusions: Polymyxins are associated with a higher risk of nephrotoxicity than non–polymyxin-based regimens. **Florian Wagenlehner, Clin Microbiol Infect 2021;27:671**

Introduction

Polymyxins such as colistin and polymyxin B are lipopeptide antibiotics with broad activity against Gram-negative bacteria. After their introduction in the 1950s, their use declined in the 1970s as a result of widely reported adverse effects of nephrotoxicity and neurotoxicity [1]. However, the rising incidence of multidrug-resistant Gram-negative infections with limited therapeutic options has resulted in increased reliance on polymyxin therapy [2]. Rates of nephrotoxicity and neurotoxicity during polymyxin treatment vary widely between reports [1]. Therefore, there is a need for clarity and an understanding of the factors that influence their incidence.

A meta-analysis of 95 observational studies in patients who received parenteral polymyxins showed nephrotoxicity prevalence was 26.7% (95% confidence interval (CI) 22.8–30.9) for colistin and 29.8% (95% CI 23.8–36.7) for polymyxin B [3]. Notably, this study did not include randomized controlled trials, and searches were limited to reports through September 2016. Another recent meta-analysis of 20 comparative studies showed that colistin was associated with higher rates of acute kidney injury (AKI) than other antibiotics (odds ratio (OR) 1.82 (95% CI 1.13–2.92)) [4]. However, to our knowledge, detailed meta-analyses to identify patient- or treatment-related risk factors for nephrotoxicity have not previously been reported. Rates of neurotoxicity during polymyxin therapy are reported less frequently than for nephrotoxicity and are generally much lower (<7%); symptoms tend to be mild in severity [5]. To our knowledge, meta-analyses of neurotoxicity rates have not been published.

The objective of this systematic review was to estimate the incidence of nephrotoxicity and neurotoxicity associated with polymyxin treatment and assess factors such as baseline renal function, dosing regimen or the use of concomitant drugs which may influence these.

Methods

This systematic review was undertaken according to the principles outlined in the Cochrane handbook and guidance published by the Centre for Reviews and Dissemination. The protocol was published in the PROSPERO (International Prospective Register of Systematic Reviews) database (CRD42019134926).

Eligibility criteria

Literature searches of Medline, Embase and the Cochrane Library using online search tools (ncbi.nlm.nih.gov/pubmed, embase.com and cochranelibrary.com) were undertaken to identify studies reporting the rate of nephrotoxicity and/or neurotoxicity in hospitalized patients treated with colistin and/or polymyxin B for the treatment of bacterial infections. The PubMed search strategy is provided in Supplementary Table S1. Studies were excluded if they reported polymyxin use in oral or ophthalmologic applications, as plasma accumulation and systemic toxicity were not anticipated. Systematic reviews, non–systematic reviews, meta-analyses and studies reported in languages other than English were excluded.

Study selection and data extraction

Two reviewers independently screened titles and abstracts for inclusion on the basis of the eligibility criteria, then independently assessed full text of potentially relevant publications; a third reviewer resolved conflicts. Where results for one study were reported in more than one article, related studies were grouped to ensure that participants were only included once.

One reviewer extracted relevant data from eligible studies using a piloted data extraction form, and a second reviewer verified every data point. Supplementary Table S2 lists the data extraction elements. The risk of bias was assessed using the relevant tool for each study design (Newcastle Ottawa Scale for cohort and case–control studies and the Cochrane Risk of Bias tool for randomized controlled trials).

Synthesis and analysis

Raw data of numbers of nephrotoxic or neurotoxic events were statistically pooled, where appropriate. Where multiple nephrotoxicity outcomes were reported, events defined by internationally recognized criteria (Risk, Injury, Failure, Loss, End-stage kidney disease (RIFLE), Acute Kidney Injury Network (AKIN) or Kidney Disease Improving Global Outcomes (KDIGO)) were selected in preference to other outcomes. Where a study reported the number of patients with kidney injury across multiple time points, the highest reported nephrotoxicity rate was chosen (either during treatment or at end of treatment) to obtain the rate of nephrotoxicity at any time during treatment. Some studies reported rates by number of patients and others by treatment episodes; however, because the number of patients with more than one treatment episode was usually very low, both types of data were included in analyses.

Meta-analyses were performed using Comprehensive Meta-analysis (Biostat, Englewood, NJ, USA). Raw data of event number and sample size (unadjusted) were analysed using a random-effects model to calculate the overall event rate and 95% CI. Studies were weighted using the inverse variance method. Between-trial heterogeneity was estimated using the inconsistency relative index I^2, which describes the percentage of total variation across studies that is due to heterogeneity rather than chance [6]. Prespecified subgroup meta-analyses were conducted where data permitted using a mixed-effects model; reported p values correspond to the hypothesis that event rate does not differ across subgroups. ORs and 95% CIs were calculated in pairwise analyses using random effects models and raw data of event numbers and sample sizes. Sensitivity analyses were performed for all meta-analyses using the leave-one-out method in order to determine whether one particular study affected pooled estimates.

Results

Study and patient characteristics

Literature searches conducted on 2 January 2020 identified 1597 unique records for screening. Of these, 237 studies, reported in 240 publications, met the inclusion criteria (Fig. 1). Only four of the

included studies were published before 2000; all other publications reporting polymyxin-associated toxicity before this date were case reports or studies in healthy volunteers. The characteristics of the 237 included studies are listed in Supplementary Table S4; a summary is shown in Tables 1 and 2. Fifteen of the studies were randomized trials [7–21], 11 were case–control studies [22–32] and 211 were cohort studies [33–63, 64–94, 95–125, 126–156, 157–187, 188–218, 219–243].

Nephrotoxicity

Across all studies, 10,285 nephrotoxic events in 35,569 patients receiving polymyxins were analysed. The overall nephrotoxicity rate was 0.282 (95% CI 0.259–0.307; Fig. 2(a) and Supplementary Fig. S2); the rate of severe nephrotoxicity (defined as RIFLE grade of 'failure' or above, AKIN grade 3 or KDIGO grade 3) was 0.131 (95% CI 0.114–0.151; Fig. 2(a) and Supplementary Fig. S3). Forty-six

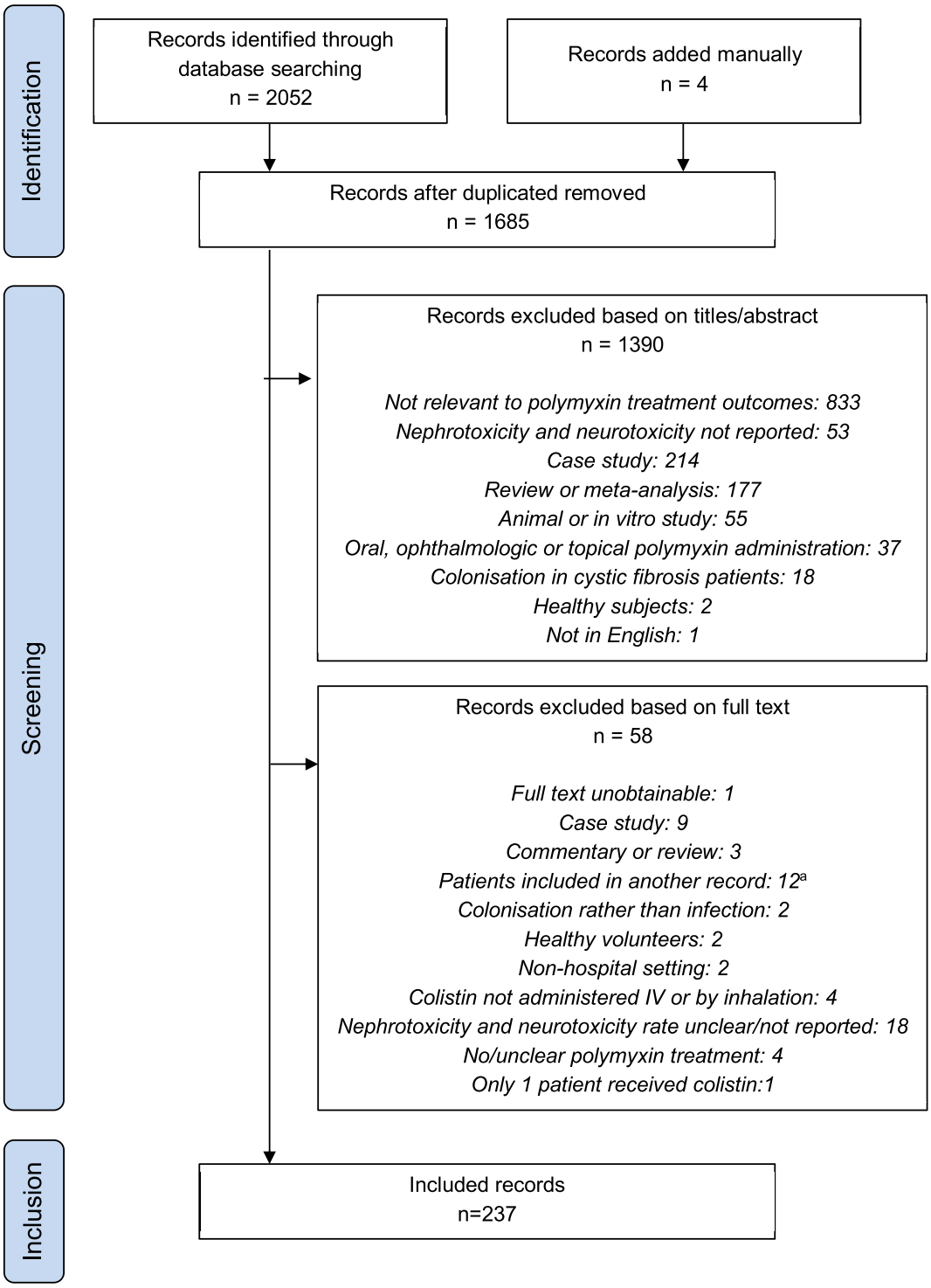


Fig. 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analysis) flow diagram. [a]Three records reported additional relevant data for included studies; these data were therefore pooled for analyses.

Table 1
Summary of study characteristics

Study characteristic	All studies ($N = 237$)	Secondary analysis population ($N = 128$)
Study design, *n* (%)		
Retrospective cohort	158 (67)[a]	84 (66)[b]
Prospective cohort	57 (24)[a]	33 (26)[b]
Randomized controlled trial	15 (6)	9 (7)
Case–control study	11 (5)	4 (3)
Location, *n* (%)		
Africa	7 (3)	1 (0.8)
Asia	57 (24)	30 (23)
Europe	45 (19)	21 (16)
Middle East	58 (24)	34 (26)
North America	44 (19)	28 (21)
South America	20 (8)	9 (7)
International	5 (2)	4 (3)
Unknown	1 (0.4)	1 (0.8)
No. of centres in study, *n* (%)		
Single centre	187 (79)	95 (74)
2–10 centres	36 (15)	24 (19)
>10 centres	6 (3)	4 (3)
Unknown	8 (3)	5 (4)
Sample size, *n* (%)		
<50 patients	82 (35)	32 (25)
50 to <100 patients	65 (27)	33 (26)
100 to <500 patients	86 (36)	62 (48)
≥500 patients	4 (2)	1 (0.8)
Polymyxin provided, *n* (%)		
Colistin	196 (83)[c]	104 (81)
Polymyxin B	28 (12)	14 (11)
Colistin or polymyxin B	13 (5)[d]	10 (8)[e]
Length of polymyxin therapy in days		
Range across studies	0 to 139	3 to 96
Range of study medians	5 to 20	6 to 13.5

[a] Three sudies involved both prospective and retrospective cohorts.
[b] Two sudies involved both prospective and retrospective cohorts.
[c] In one study, the form of colistin used was colistin sulphate but in all other studies colistimethate sodium was reported or assumed, to be used.
[d] Four studies reported data in patients receiving either colistin or polymyxin B and nine studies reported outcomes for both patients receiving colistin and those receiving polymyxin B.
[e] Four studies reported data in patients receiving either colistin or polymyxin B and six studies reported outcomes for both patients receiving colistin and those receiving polymyxin B.

studies reported recovery rates after AKI during polymyxin treatment; these varied widely, ranging from 12% to 100%. Eleven of 46 studies reported recovery in more than 90% patients [38,57,96,136,152,200,204,223,225,228,244], 17 of 46 studies reported recovery rates of 50–90% [7,8,34,48,63,67,68,71,74,84,115,117,183,187,220,222,240] and 18 of 46 studies reported recovery in ≤50% patients [13,58,67,79,91,104,112,130,148,151,156,162–164,198,201,208,245]. However, it should be noted that studies differed in the criteria used to define recovery (return to baseline, return to within normal range, no longer meeting criteria for AKI or undefined), the time period of follow-up (end of treatment to 1 year, where given) and the way in which missing data were handled.

Thirty-three studies compared nephrotoxicity rates in patients receiving polymyxins with those receiving other therapies [9,12,13,15,19,23,25,29,54,65,73,74,104,105,109,117,127,135,146,150,154,158,164,184,188,197,205,207,208,211,216,241]. Meta-analysis showed that polymyxin-based therapy was associated with a higher rate of nephrotoxicity than non–polymyxin-based therapies (OR 2.23 (95% CI 1.58–3.15); $p < 0.001$; $I^2 = 65$; Fig. 3).

To investigate possible factors influencing nephrotoxicity rates during polymyxin therapy, subgroup analyses were performed. Rates of observed nephrotoxicity varied significantly by the criteria used to define the outcome (AKIN, 0.353 (95% CI 0.279–0.434); KDIGO, 0.347 (95% CI 0.270–0.433); RIFLE, 0.388 (95% CI 0.358–0.420); 'other', 0.155 (95% CI 0.127–0.188); $p < 0.001$; Fig. 2(a) and Supplementary Fig. S4). A significant difference in the nephrotoxicity rate was also shown between patients receiving inhaled-only and systemic polymyxins (0.138 (95% CI 0.091–0.202) and 0.295 (95% CI 0.270–0.321), respectively; $p < 0.001$; Fig. 2(a) and Supplementary Fig. S5).

As a result of the impact of assessment criteria and administration route on observed nephrotoxicity rates, subsequent subgroup analyses of the nephrotoxicity rate were performed in a secondary analysis population that included only studies using internationally recognized assessment criteria (RIFLE, AKIN or KDIGO) and excluded ten studies in which less than 50% patients received systemic polymyxins [19,26,53,66,71,119,143,147,155,243]. The results of these subanalyses are presented here, whereas meta-analyses of the nephrotoxicity rate including all 237 studies regardless of AKI criteria and administration route are presented in Supplementary Figs S1 to S17. Pairwise meta-analyses of within-study comparisons were performed with all studies meeting the eligibility criteria for the review. Study characteristics of the 128 studies included in the secondary analysis population are presented in Tables 1 and 2. The overall rate of nephrotoxicity across these studies was 0.391 (95% CI 0.364–0.419), and the rate of severe nephrotoxicity was 0.132 (95% CI 0.114–0.151; Fig. 2(b) and Supplementary Figs S19 and S20).

In subgroup analysis by polymyxin, nephrotoxicity rates were not significantly different between patients treated with colistin and polymyxin B (0.393 (95% CI 0.362–0.425) and 0.381 (95% CI 0.324–0.441), respectively; p 0.728; Fig. 2(b) and Supplementary Fig. S21). However, pairwise meta-analysis across all studies directly comparing nephrotoxicity rates in patients receiving colistin and those receiving polymyxin B showed significantly higher rates of nephrotoxicity with colistin (OR 1.65 (95% CI 1.16–2.35); p 0.005; Table 3 and Supplementary Fig. S33).

The nephrotoxicity rate was not significantly different in patients who received a polymyxin loading dose compared to those who did not (0.391 (95% CI 0.320–0.467) and 0.438 (95% CI 0.371–0.508); p 0.363; Fig. 2(b) and Supplementary Fig. S22). However, in pairwise meta-analysis of all studies reporting nephrotoxicity in both patients receiving and those not receiving a loading dose, the odds of nephrotoxicity were significantly higher in patients who received a loading dose (OR 1.833 (95% CI 1.189–2.826); p 0.006; Table 3 and Supplementary Fig. S34).

Therapeutic doses varied greatly across the studies: for example, where intravenous colistin maintenance dosages for patients with normal renal function were reported in million Internation Units (MIU) per day, the daily dose ranged from 1 to 36 MIU. Sixteen studies in the secondary analysis population reported nephrotoxicity rates in subgroups of patients by polymyxin dose [10,17,30,52,92,106,108,113,130,151,181,198,206,215,221,232]; cutoffs varied between studies but were used to create high, intermediate and low dose subgroups that, in general, corresponded to intravenous colistin doses of more than 9 MIU per day, 6–9 MIU per day and less than 6 MIU per day, respectively (Supplementary Table S3). There was a significant difference in the rate of nephrotoxicity between subgroups of patients receiving high, intermediate and low polymyxin doses (0.446 (95% CI 0.367–0.528), 0.374 (95% CI 0.280–0.478) and 0.284 (95% CI 0.224–0.352), respectively; p 0.001; Fig. 2(b) and Supplementary Fig. S23). This result was supported by pairwise analysis of all studies reporting nephrotoxicity rates in patients treated with different polymyxin doses, which showed that higher doses were associated with increased odds of nephrotoxicity compared to lower doses (OR 1.89 (95% CI 1.40–2.55); $p < 0.001$; Table 3 and Supplementary Fig. S35).

A significant difference in nephrotoxicity rates was found between age groups (neonates: 0.190 (95% CI 0.073–0.412),

Table 2
Summary of patient characteristics

Characteristic	All studies ($N = 237$)	Secondary analysis population ($N = 128$)
Age, *n* (%)		
Neonates	7 (3)	1 (0.8)
Paediatrics	18 (8)	3 (2)
Adult	145 (61)	100 (78)
Age >65 years	1 (0.4)	1 (0.8)
Children and adults	66 (28)	23 (18)
Range across studies	23 gestational weeks to 103 years	23 gestational weeks to 88 years
Range of study medians	28 gestational weeks to 77 years	28 gestational weeks to 71 years
Female, range across studies	0–79%	3–63%
Baseline creatinine (mg/dL)		
Range across studies	0.1 to 9.8	0.1 to 4.7
Range of study medians	0.2 to 1.5	0.4 to 1.5
Infection site, *n* (%)		
Mixed	157 (66)	91 (71)
Respiratory infection	50 (21)	19 (15)
Bacteraemia/sepsis	22 (9)	14 (11)
Burns	2 (0.8)	0
Urinary tract	2 (0.8)	2 (2)
Postsurgical intra-abdominal	1 (0.4)	1 (0.8)
Surgical site	1 (0.4)	0
Central nervous system	1 (0.4)	0
Mediastinitis	1 (0.4)	1 (0.8)
Causative pathogen, *n* (%)		
Unspecified Gram-negative bacteria	60 (25)	35 (27)
Acinetobacter	61 (26)[a]	34 (27)[b]
Pseudomonas	28 (12)[a]	12 (9)[b]
Klebsiella	11 (5)[a]	4 (3)[b]
Enterobacterales	2 (0.8)	1 (0.8)
Unspecified	97 (41)	57 (45)

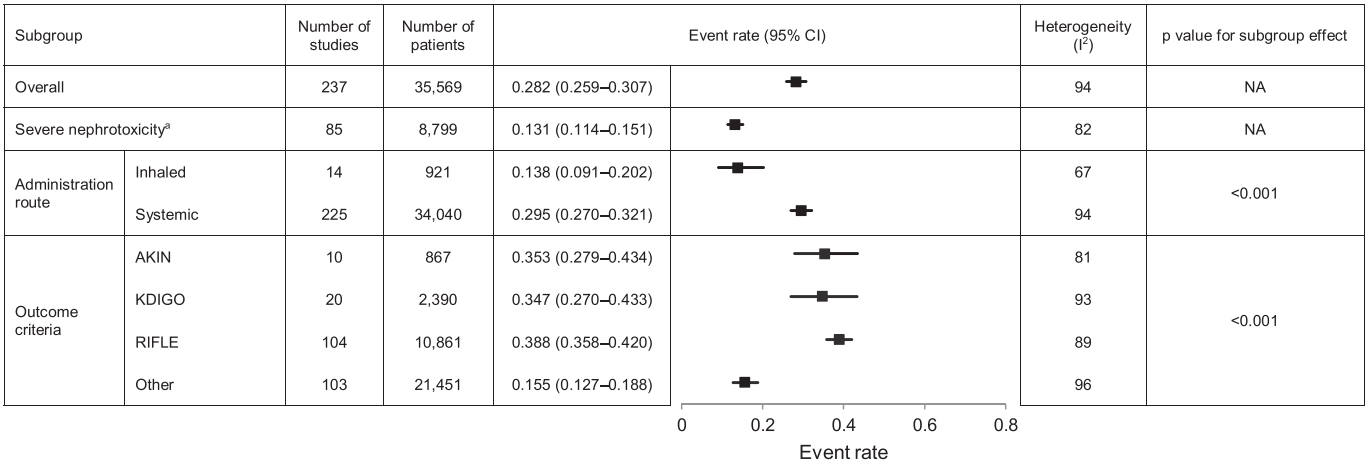
[a] Ten studies were carried out in patients with *Acinetobacter* or *Pseudomonas* infections and six studies included patients with *Klebsiella*, *Acinetobacter* or *Pseudomonas* infections.
[b] Three studies were carried out in patients with *Acinetobacter* or *Pseudomonas* infections and three studies included patients with *Klebsiella*, *Acinetobacter* or *Pseudomonas* infections.

paediatrics: 0.097 (95% CI 0.011–0.499), younger adults (upper limit ranged from 51–65 years across studies): 0.390 (95% CI 0.309–0.478), older adults (lower limit ranged from 51–65 years across studies): 0.506 (95% CI 0.382–0.629), respectively; p 0.030; Fig. 2(b) and Supplementary Fig. S26). Across all studies reporting nephrotoxicity rates by age-related subgroups, pairwise meta-analysis showed that older patient groups had increased odds of nephrotoxicity during polymyxin treatment than younger patients (age cutoff 18–70 years across studies; OR 1.85 (95% CI 1.33–2.57); $p < 0.001$; Table 3 and Supplementary Fig. S38).

No significant difference in nephrotoxicity rate was seen between patients with impaired and normal baseline renal function (0.346 (95% CI 0.211–0.513) and 0.465 (95% CI 0.397–0.535), respectively; p 0.188; Fig. 2(b) and Supplementary Fig. S27); this result was supported by pairwise analysis across all studies comparing outcomes by baseline renal function (OR 0.94 (95% CI 0.43–2.04); p 0.866; Table 3 and Supplementary Fig. S39).

In all but two studies [54,135], some or all patients receiving polymyxins received concomitant antibiotics. A significantly lower nephrotoxicity rate was observed in patients receiving

a.



b.

Subgroup		Number of studies	Number of patients	Event rate (95% CI)	Heterogeneity (I^2)	p value for subgroup effect
Overall		128	13,554	0.391 (0.364–0.419)	89	NA
Severe nephrotoxicity[a]		84	8,787	0.132 (0.114–0.151)	82	NA
Polymyxin	Colistin	110	10,789	0.393 (0.362–0.425)	90	0.728
	Polymyxin B	21	2,354	0.381 (0.324–0.441)	86	
Loading dose	Loading dose	23	1,466	0.391 (0.320–0.467)	85	0.363
	No loading dose	25	2,557	0.438 (0.371–0.508)	90	
Dose[b]	High	18	1,035	0.446 (0.367–0.528)	84	0.001
	Intermediate	15	1,081	0.374 (0.280–0.478)	89	
	Low	18	1,411	0.264 (0.215–0.321)	75	
Setting	ICU	64	12,784	0.356 (0.314–0.401)	89	0.951
	Non-ICU	15	898	0.352 (0.239–0.485)	88	
Sex	Female	32	1,312	0.447 (0.394–0.501)	68	0.824
	Male	32	2.051	0.455 (0.410–0.500)	71	
Age[c]	Neonates	1	21	0.190 (0.073–0.412)	0	0.030
	Paediatric	2	36	0.097 (0.011–0.499)	56	
	Younger adults	8	382	0.390 (0.309–0.478)	61	
	Older adults	9	533	0.506 (0.382–0.629)	86	
Baseline renal function[d]	Impaired	6	371	0.346 (0.211–0.513)	89	0.188
	Normal	20	2,052	0.465 (0.397–0.535)	89	
Combination therapy	Monotherapy	11	594	0.218 (0.152–0.304)	68	0.015
	Combination	23	2,204	0.356 (0.286–0.433)	89	
Number of concomitant nephrotoxins	No nephrotoxins	21	1,047	0.372 (0.284–0.469)	86	0.006
	≥1 nephrotoxin	18	1,557	0.457 (0.396–0.519)	80	
	≥2 nephrotoxin	5	187	0.561 (0.489–0.631)	0	
	≥3 nephrotoxin	3	110	0.582, (0.453–0.701)	22	
Type of concomitant nephrotoxin	ACEI/ARB	7	65	0.510 (0.314–0.704)	43	0.073
	Aminoglycoside	24	476	0.476 (0.412–0.540)	36	
	Amphotericin B	9	67	0.408 (0.196–0.660)	55	
	Contrast agent	14	287	0.392 (0.285–0.511)	63	
	Diuretic	14	590	0.478 (0.401–0.555)	66	
	Glycopeptide	28	1,235	0.475 (0.420–0.530)	65	
	NSAID	10	151	0.323 (0.252–0.404)	0	
	Rifampicin	5	272	0.395 (0.256–0.555)	78	
	Vasopressor	11	456	0.518 (0.410–0.624)	73	

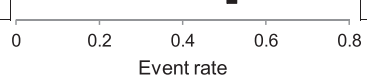


Fig. 2. Forest plot of nephrotoxicity rates in patients receiving polymyxins across all studies (a) and studies assessing nephrotoxicity by AKIN, KDIGO or RIFLE criteria and in which more than 50% patients received systemic polymyxins (b). ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval; ICU, intensive care unit; NSAID, nonsteroidal anti-inflammatory drug. [a]Outcome of RIFLE 'failure' or higher, AKIN grade 3 or KDIGO grade 3 nephrotoxicity. [b]Dose cutoffs varied across studies but in general for intravenous colistin doses >9 MIU per day = high, 6–9 MIU per day = intermediate and ≤6 MIU = low. [c]Age categories varied between studies, but the cutoff between younger and older adults ranged between 55–68 years. [d]Definitions of baseline renal impairment varied between studies, but where defined, they were based on RIFLE/KDIGO criteria or creatinine clearance (cut-offs of 60 mL/min/1.73 m^2, 80 mL/min/1.73 m^2, 50 mL/min and 90 mL/min).

Study name	Comparator	Events/sample size		Odds ratio (95% CI)	Relative weight	p value
		Polymyxin	Comparator			
Betrosian, 2008	Ampicillin/sulbactam	5/15	2/13	2.75 (0.43–17.49)	2.27	0.284
Chan, 2010	AG	4/7	6/30	5.33 (0.93–30.50)	2.45	0.060
Chuang, 2014	Tigecycline	8/84	2/84	4.32 (0.89–20.97)	2.75	0.070
Chusri, 2019	Tigecycline	10/14	3/14	9.17 (1.63–51.43)	2.48	0.012
Cisneros, 2019	Carbapenem	40/120	21/112	2.17 (1.18–3.98)	5.45	0.013
Durakovic, 2011	Unspecified	3/26	0/26	7.89 (0.39–160.91)	1.09	0.179
Garancho-Montero, 2003	Carbapenem	5/21	6/14	0.42 (0.10–1.79)	3.01	0.240
Ghafur, 2019	Meropenem or C/S	12/118	10/108	1.11 (0.46–2.68)	4.59	0.818
Gounden, 2009	AG	4/21	2/23	2.47 (0.40–15.15)	2.33	0.328
Holloway, 2006	Doxycycline	7/33	0/4	2.55 (0.12–52.83)	1.08	0.546
Ipek, 2017	Unspecified	6/47	8/59	0.93 (0.30–2.90)	3.83	0.905
John, 2019	Ceftazidime/avibactam	32/75	8/42	3.16 (1.29–7.75)	4.55	0.012
Khalili, 2018	Carbapenem	3/24	1/23	3.14 (0.30–32.65)	1.63	0.338
Kim, 2016	Tigecycline	8/40	0/30	15.95 (0.88–288.40)	1.16	0.061
Koomanachai, 2007	Unspecified	24/78	10/15	0.22 (0.07–0.72)	3.72	0.012
Kvitko, 2011	Unspecified	16/45	10/88	4.30 (1.75–10.56)	4.54	0.001
Kwon, 2014	Tigecycline	17/39	2/16	5.41 (1.08–27.09)	2.69	0.040
Lim, 2011	Unspecified	10/20	10/35	2.50 (0.80–7.84)	3.81	0.116
McKinnell, 2019	Plazomicin	8/16	2/12	5.00 (0.82–30.46)	2.34	0.081
Miano, 2018	Unspecified	77/150	33/150	3.74 (2.26–6.18)	5.77	<0.001
Mosaed, 2018	Ampicillin/sulbactam	6/11	1/12	13.20 (1.24–140.68)	1.60	0.033
Motsch, 2019	Carbapenem	13/16	6/29	16.61 (3.55–77.78)	2.83	<0.001
Oliviera, 2008	Ampicillin/sulbactam	18/69	21/81	1.01 (0.49–2.10)	5.07	0.982
Ozscurekci, 2016	Quinilone or BL	3/73	2/30	0.60 (0.10–3.79)	2.28	0.587
Pogue, 2019	AG or ceftozolane/tazobactam	24/56	16/144	6.00 (2.86–12.60)	5.03	<0.001
Rattanaupawan, 2010	Unspecified	13/51	11/49	1.18 (0.47–2.97)	4.47	0.722
Rocco, 2013	Unspecified	57/147	54/132	0.92, (0.57–1.48)	5.83	0.716
Salahuddin, 2017	AG or vancomycin	48/97	128/280	1.16 (0.73–1.85)	5.87	0.521
Shields, 2017	Unspecified	13/30	16/79	3.01 (1.22–7.46)	4.51	0.017
Zalts, 2016	Ampicillin/sulbactam	1/66	0/32	1.49 (0.06–37.56)	0.97	0.809
Overall				2.23 (1.58–3.15)		<0.001

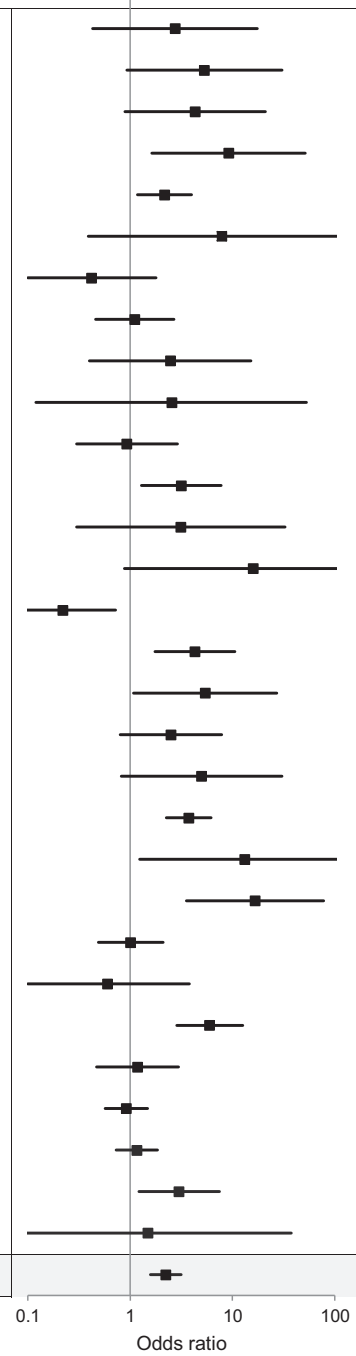


Fig. 3. Forest plot of nephrotoxicity rates in patients receiving polymyxins compared to patients receiving non–polymyxin-based treatment regimens. AG, aminoglycoside; BL, β-lactam; CI, confidence interval; C/S, cefoperazone/sulbactam.

polymyxin monotherapy compared to those receiving combination therapy (0.218 (95% CI 0.152–0.274) and 0.356 (95% CI 0.286–0.433), respectively; p 0.015; Fig. 2(b) and Supplementary Fig. S28). Concomitant antibiotics used in combination regimens were most commonly unspecified (34%) or β-lactams (30%). However, across all studies reporting nephrotoxicity rates in patients receiving polymyxin monotherapy and those receiving combination therapy (concomitant antibiotics unspecified in 55% of included studies and β-lactams in 27%), nephrotoxicity rates were not significantly affected by combination therapy (OR 1.36 (95% CI 0.87–2.15); p 0.181; Table 3 and Supplementary Fig. S40).

Patients receiving polymyxins are often seriously ill and receiving multiple drugs, some of which may be nephrotoxic. Rates

Table 3
Summary of pairwise comparative analyses

Comparison	No. of studies	No. of patients	OR (95% CI)	p
Systemic vs. inhaled	10	741 vs. 649	3.56 (1.70–7.44)	0.001
Colistin vs. polymyxin B	9	4934 vs. 1670	1.65 (1.16–2.35)	0.005
Loading dose vs. no loading dose[a]	11	670 vs. 604	1.83 (1.19–2.83)	0.006
Higher vs. lower dose	23	1438 vs. 1948	1.89 (1.40–2.55)	<0.001
ICU vs. non-ICU	17	1503 vs. 909	1.55 (1.02–2.37)	0.042
Female vs. male	37	3639 vs. 5221	0.91 (0.79–1.04)	0.148
Older age vs. younger age[b]	13	579 vs. 489	1.85 (1.33–2.57)	<0.001
Impaired vs. normal baseline renal function[c]	7	350 vs. 578	0.94 (0.43–2.04)	0.866
Combination therapy vs. monotherapy	11	1024 vs. 576	1.36 (0.89–2.15)	0.181
Concomitant nephrotoxin vs. none	22	3165 vs. 4339	1.19 (0.90–2.15)	0.226
With vs. without specified nephrotoxins				
ACE inhibitor/ARB	11	93 vs. 1138	1.61 (0.89–2.91)	0.118
Aminoglycoside	29	571 vs. 2363	1.17 (0.88–1.55)	0.293
Amphotericin B	12	86 vs. 1814	1.36 (0.76–2.41)	0.302
Contrast agent	18	334 vs. 1699	1.07 (0.74–1.56)	0.705
Diuretics	18	811 vs. 1339	2.19 (1.63–2.94)	<0.001
Glycopeptide	34	1393 vs. 2603	1.63 (1.31–2.03)	<0.001
NSAIDs	14	222 vs. 1898	0.79 (0.55–0.14)	0.208
Rifampicin	7	339 vs. 894	1.06 (0.79–1.44)	0.684
Vasopressor	12	531 vs. 1223	1.71 (1.09–2.68)	0.019

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CI, confidence interval; ICU, intensive care unit; NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio.

[a] Dose cutoffs varied across studies but in general, for intravenous colistin doses, >9 million International Units (MIU) per day was high; 6–9 MIU per day, intermediate; and ≤6 MIU per day, low.

[b] Age categories varied between studies but where defined, the cutoff between younger and older adults ranged from 55–70 years old.

[c] Definitions of baseline renal impairment varied between studies but where defined, were based on Risk, Injury, Failure, Loss, End-stage kidney disease (RIFLE)/Kidney Disease Improving Global Outcomes (KDIGO) criteria or creatinine clearance (cutoffs of 60 mL/min/1.73 m^2, 80 mL/min/1.73 m^2, 50 mL/min and 90 mL/min).

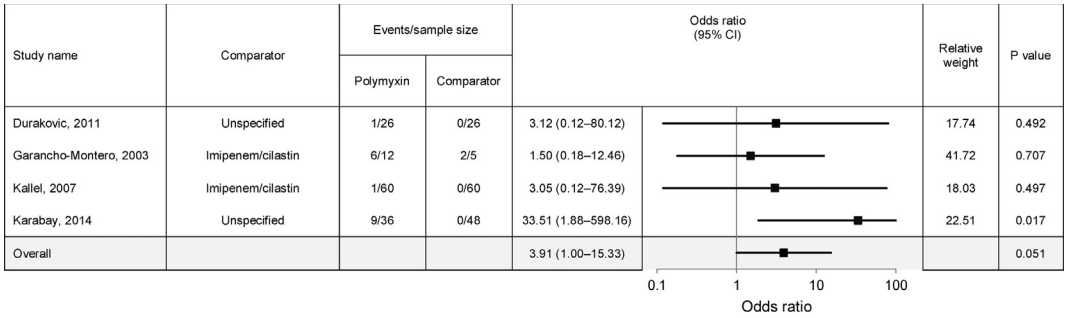


Fig. 4. Forest plot of neurotoxicity rates in patients receiving polymyxins compared to patients receiving non–polymyxin-based treatment regimens. CI, confidence interval.

of nephrotoxicity during polymyxin treatment varied significantly across groups receiving different numbers of concomitant nephrotoxins (none: 0.372 (95% CI 0.284–0.469); ≥1: 0.457 (95% CI 0.396–0.519); ≥2: 0.561 (95% CI 0.489–0.631); ≥3: 0.582 (95% CI 0.453–0.701); p 0.006; Fig. 2(b) and Supplementary Fig. S29). In pairwise analysis of studies reporting outcomes with and without any concomitant nephrotoxins, no significant difference in nephrotoxicity rate was observed (OR 1.19 (95% CI 0.90–1.58); p 0.226; Table 3 and Supplementary Fig. S41). However, in subgroup analysis by type of nephrotoxin, the odds of nephrotoxicity were significantly higher for patients receiving diuretics, glycopeptides and vasopressors than for those that did not (p < 0.001, <0.001 and 0.019, respectively; Table 3 and Supplementary Fig. 42). Use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, aminoglycosides, amphotericin B, contrast agents, nonsteroidal anti-inflammatory drugs or rifampicin did not significantly affect the odds of nephrotoxicity (Table 3 and Supplementary Fig. S42).

Neurotoxicity

Seventy studies reported the rate of neurotoxicity in patients receiving polymyxin therapy [7,8,11,19,21,23,25,26,28,30,37,45,48,50,54,57,59,62,63,66,68,71,72,77,85,88,94,95,98,99,102,104,110,117,120,126,128,131,132,134,140,150,155,157,163,176,182,188,189,191,199,205,210,217,219,225,228,231,246]. The majority of articles failed to outline criteria used to determine neurotoxicity (38/70); where defined, criteria varied but usually included seizure, muscle weakness, paraesthesia, ataxia and altered mental status. However, some studies also classed less severe symptoms such as headache or irritability as neurotoxicity [51,72,135,204].

Polymyxin-based therapy was associated with a numerically but not statistically significantly higher rate of neurotoxicity than non–polymyxin-based therapies (OR 3.91 (95% CI 1.00–15.33); p 0.051; $I^2 = 0$; Fig. 4). The overall rate of neurotoxicity was 0.030 (95% CI 0.020–0.043; Fig. 5(a) and Supplementary Fig. S16). In order to determine the rate of neurotoxicity associated with systemic polymyxin treatment, studies in which less than half of patients received systemic polymyxins [19,26,53,66,71,119,155] were excluded; in this analysis, the rate of neurotoxicity was 0.032 (95% CI 0.022–0.048); Fig. 5(b) and Supplementary Fig. S30). No significant difference in the rate of neurotoxicity was observed in subgroup analysis of patients receiving colistin and polymyxin B (0.028 (95% CI 0.019–0.043) and 0.036 (95% CI 0.022–0.060), respectively; p 0.480; Fig. 5(a) and Supplementary Fig. S17).

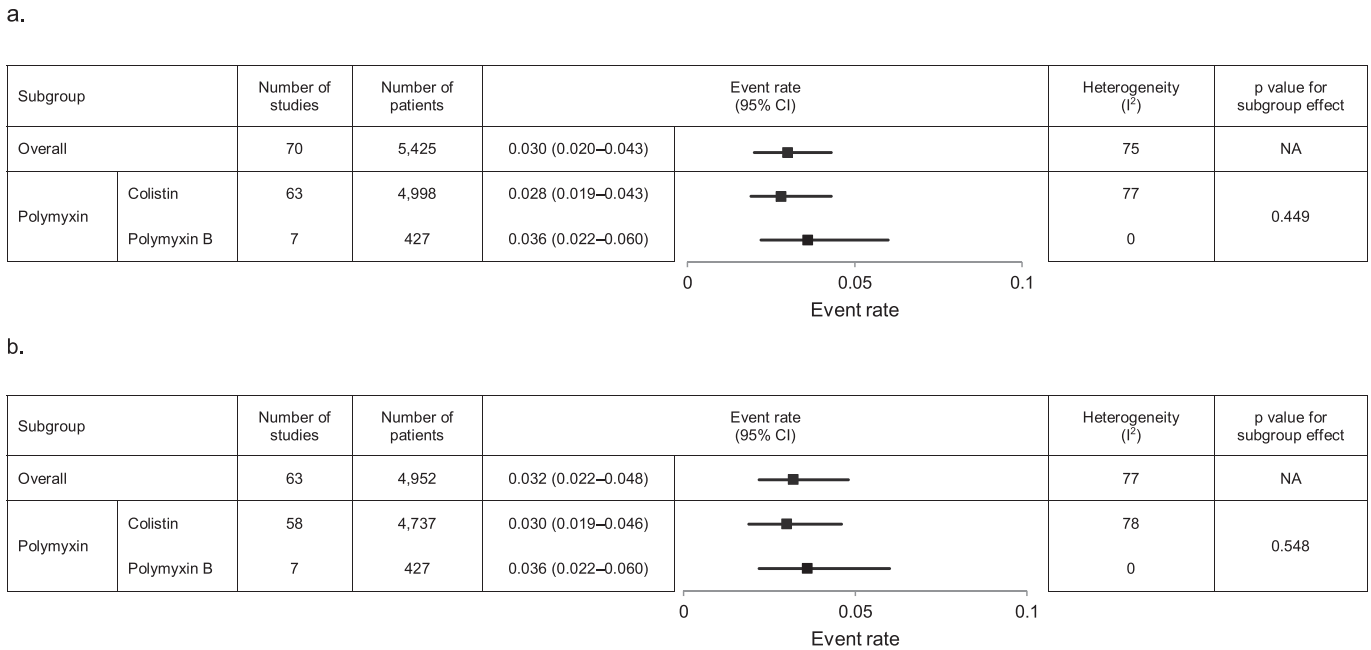


Fig. 5. Forest plot of neurotoxicity rates in patients receiving polymyxins across all studies (a) and studies in which more than 50% patients received systemic polymyxins (b). CI, confidence interval.

Quality and bias

Nearly all included studies were conducted in specific patient groups; only 11 studies did not restrict patients by age, infection or comorbidities [32,69,76,94,95,128,145,172,186,203,211]. In observational studies comparing the toxicity of polymyxins with that of other treatments, there was nearly always a lack of comparability between groups. Assessors of toxicity outcomes were unaware of the received treatments in very few of the included studies, and the length and adequacy of follow-up was often unclear.

Leave-one-out sensitivity analyses of each analysis did not identify any study that affected pooled estimates. Analysis of study-size bias using funnel plots showed significant asymmetry, with smaller trials likely to report lower rates of nephro- and neurotoxicity (Egger bias −1.29 (95% CI −2.07 to −0.51); p 0.001 and −1.56 (95% CI −2.34 to −0.79); $p < 0.001$, respectively; Supplementary Fig. S43).

Discussion

Drug-induced nephrotoxicity is recognized as a common complication in the treatment of critically ill patients that contributes to morbidity and increased healthcare utilization, with 14% to 26% adults in the intensive care unit reported to be affected by AKI [247–249].

In our systematic review and meta-analysis, we confirm that polymyxin therapy is associated with a higher risk of nephrotoxicity than other therapies (OR 2.23 (95% CI 1.58–3.15)), which is consistent with other analyses [4]. A doubled odds of developing renal toxicity is clinically relevant because it is an important endpoint, given the association between development of AKI and increased length of stay, long-term renal failure and/or death [247–249,264]. The overall nephrotoxicity rate in patients treated with polymyxins (28.1% (95% CI 25.9–30.7)) is comparable to that reported previously (27.6% (95% CI 24.3–30.9) [3] and, as previously reported [3,4,224], rates of nephrotoxicity were found to be influenced by assessment criteria. Restriction to studies using internationally recognized AKIN, KDIGO or RIFLE criteria showed a much higher rate of observed nephrotoxicity during systemic polymyxin therapy (39.1% (95% CI 36.4–41.9)), which is likely to be closer to the true rate than previously reported. This review also showed a substantial risk of severe and long-term renal damage for patients treated with polymyxins, with a rate of severe nephrotoxicity of 13.1% (95% CI 11.4–15.1) and 39% of studies reporting recovery rates of less than 50%.

Although no significant difference in rates of nephrotoxicity assessed by internationally recognized criteria was seen between patients treated with systemic colistin and polymyxin B, pairwise analyses of comparative studies showed a lower rate of nephrotoxicity with polymyxin B, consistent with previous meta-analyses [4,250]. It should be noted that all of these meta-analyses include some studies in which polymyxin B doses were adjusted on the basis of renal function, which is not included in current recommendations [251]. However, a lower risk of nephrotoxicity with polymyxin B compared to colistin is widely accepted and is likely to be a result of differing pharmacokinetic properties [1,251–253].

As a result of differences in dosing strategy, meta-analyses using mixed-effects models to investigate the effect of polymyxin dose on nephrotoxicity rates have not previously been performed, although assimilation of patient data from 19 studies showed that higher doses are associated with higher rates of nephrotoxicity [1]. The results presented here show that higher polymyxin doses are associated with a higher risk of nephrotoxicity (OR 1.96 (95% CI 1.46–2.63)); however, it should be noted that data regarding the efficacy of differing doses were not considered. Our analysis is consistent with histopathology in animal models, which shows that polymyxin nephrotoxicity is dose dependent and related to acute tubular damage of necrotic nature at the level of the proximal tubule cells [254]. Use of a loading dose is recommended when commencing colistin treatment [251], but its influence on nephrotoxicity has not been conclusively shown [1,255]. In our analyses, the nephrotoxicity risk associated with loading doses was unclear: subgroup analysis showed no significant difference in nephrotoxicity rate between studies with and without use of a loading dose,

and although pairwise analysis of comparison studies showed a significantly higher nephrotoxicity rate in patients who received a loading dose, these patients often also received a higher maintenance dose than patients who did not. Further studies in which confounding factors are comparable between groups are required to determine whether polymyxin loading doses are associated with an increased risk of AKI. Polymyxins accumulate in proximal renal tubule cells using active transport and endocytosis systems located in the luminal border of the epithelial cell [256], so we can hypothesize that the reabsorption of polymyxins can become saturated, as occurs with aminoglycosides, resulting in intracellular concentration being independent from peak serum concentration.

In contrast to some previous reports [257], sex and baseline renal impairment were not found to affect nephrotoxicity. Dose adjustment of colistin is recommended in patients with renal impairment [251] and was allowed in almost all included studies. Our results suggest that this strategy is sufficient to prevent an increased risk of AKI in patients with reduced renal function. Age is regarded as an important factor for drug-induced nephrotoxicity [258], and results from several studies support the view that older age is associated with a higher risk of polymyxin-associated nephrotoxicity [255]. In this study, meta-analyses showed that older age increases the risk of nephrotoxicity (OR 1.85 (95% CI 1.33–2.57)), and the rate of nephrotoxicity was found to be 50.6% (95% CI 38.2–62.9) in older adult patients (lower limit 51–65 years across studies). Consistent with our results, previous meta-analyses in paediatric and infant populations have shown low AKI rates during colistin therapy of 6.2% and 5.8% [259,260]. It should be noted that although very small numbers of studies in neonatal and paediatric patients were included in the secondary analysis, this was primarily because few studies in these populations used internationally recognized criteria for nephrotoxicity. In the per-protocol analysis, including all studies regardless of outcome criteria, a significant effect of age was also observed.

Although some previous meta-analyses have suggested that polymyxin combination therapies have a nephroprotective effect compared to monotherapy [4,261], others have suggested that there is no effect [262,263]. The analyses presented in this study do not support a nephroprotective effect of combination therapy. Although pairwise analysis of studies providing comparisons of nephrotoxicity rate with and without any concomitant nephrotoxins did not show any significant effect, a significant effect on nephrotoxicity rate was found in subgroup analyses by number of concomitant nephrotoxins (p 0.006). The cumulative effects of multiple nephrotoxins have been shown previously in a non–polymyxin-specific meta-analysis in which each nephrotoxic medication administered to a patient was associated with 53% greater odds of developing drug-induced nephrotoxicity [258]. Differences in the risk of nephrotoxicity during polymyxin treatment varied significantly depending on the use of different concomitant nephrotoxins (p 0.001). Use of concomitant diuretics, vasopressors and glycopeptide antibiotics were associated with increased risk of nephrotoxicity with polymyxin treatment, which is consistent with existing recommendations to avoid these where possible [251].

Neurotoxicity rates were not widely reported, so there were insufficient data to detect a significant difference in neurotoxicity rates for patients treated with polymyxins compared to those receiving other therapies. The overall observed neurotoxicity rate of 3.0% is likely an underrepresentation of the true rate as a result of difficulties in detection of neurotoxicity in a seriously ill patient population in which a high proportion of patients are unconscious or sedated.

Although meta-analyses of the rate of nephrotoxicity during polymyxin treatment have recently been reported [3,4], this systematic review is more extensive because it includes recent data from all study types, resulting in a much larger analysis population (35,569 patients vs. 4984 or 7911 patients), provides more detailed assessment of risk factors for nephrotoxicity and includes analyses of neurotoxicity. However, this study had several limitations. As a result of the volume of literature on infections, a pragmatic approach was taken in the search strategy to balance precision and sensitivity, but some relevant studies may not have been captured. For reasons of feasibility, searches were limited to studies published in English. Subsequent searches without this restriction identified seven potentially relevant single-arm studies published in languages other than English that were not included in analyses, which may have influenced results; however, this is unlikely because they involved only 272 patients in total. A pragmatic and generally accepted approach to data extraction was taken to ensure practicality, in which a single reviewer conducted the data extraction and second reviewer checked all the data points; however, it is acknowledged that the optimal approach is double independent data extraction with a third reviewer resolving any discrepancies. Combining results from randomized and nonrandomized studies is generally not recommended. However, in this study, the majority of analyses are performed using event-rate data for toxicity in a single cohort/study arm, and heterogeneity between studies was considered likely to be influenced to a greater extent by factors such as patient populations and outcome criteria than by basic study design. In support of this notion, subgroup analysis of both nephrotoxicity and neurotoxicity rates by study design (case–control, cohort and randomized trial) did not show a significant influence of study design (p 0.108 and 0.621, respectively). For analyses comparing toxicity rates between polymyxins and other therapies, where use of randomization and blinding could have influenced results, meta-analyses showed that study design did not affect the OR for nephrotoxicity or neurotoxicity (p 0.476 and 0.728). During meta-analyses of comparative studies, both-armed zero-event studies were automatically excluded. Although this strategy is widely accepted, there is no consensus regarding whether it is the most reliable methodology, and the effect on pooled estimates of the risk of toxicity, particularly neurotoxicity for which four (50%) of eight studies were excluded, is unclear. For subgroup analyses of nephrotoxicity rate by age and by polymyxin dose, cutoff values for each subgroup varied between studies. Studies were generally performed in complex patients, so it is generally not possible to assign causality of any kidney injury or neurologic event to polymyxin therapy. There was a large variation between studies in patient populations, time of assessment, polymyxin dosages, how missing data were handled and criteria for outcome assessment, although between-study differences in nephrotoxicity assessment were reduced by use of a secondary analysis population using only RIFLE, AKIN and KDIGO criteria. Many studies did not report information regarding variables of interest. In comparative analyses, there was a general lack of comparability of confounding factors between groups. The asymmetry of funnel plots showing study-size bias suggest that some of the smaller included studies may have been of lower quality with less rigorous monitoring of patients for toxicity, so actual rates of nephrotoxicity and neurotoxicity during polymyxin therapy may be higher than those reported here.

This meta-analysis of English-language studies confirms that polymyxins are associated with a greater risk of nephrotoxicity than other therapies. It suggests that the rate of nephrotoxicity assessed by internationally recognized criteria in patients treated with systemic polymyxins is as high as 39%, with 13% of patients experiencing severe nephrotoxicity. This clearly highlights a need for alternative, less toxic therapies to treat multidrug-resistant Gram-negative infections.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2020.12.009.

Transparency declaration

This study was funded by Shionogi BV. FW declares personal fees and other for advisory board attendance and study participation from Achaogen, Bionorica, OM Pharma/Vifor Pharma and Shionogi. He received personal fees for advisory board attendance from AstraZeneca, Janssen, LeoPharma, MerLion, MSD, Pfizer, RosenPharma, VenatoRx and GSK. He also reports personal fees for study participation from Enteris BioPharma and Helperby Therapeutics, as well as personal fees and other for study participation from Klosterfrau Healthcare Group. FP participated in speaker bureau for Angelini, Basilea Pharmaceutica, Gilead, Hikma, MSD, Nordic Pharma, Pfizer and Sanofi Aventis and in advisory boards for Angelini, Basilea Pharmaceutica, Correvio, Gilead, MSD, Nordic Pharma, Novartis, Pfizer and Thermo-Fisher. AS reports grants and personal fees from Pfizer and personal fees for consultancy from MSD, Menarini and Shionogi. VS is an employee of Ashfield Healthcare communications, which received funding from Shionogi BV to conduct the study. ASH is a contractor for Shionogi BV. CL is an employee of Shionogi BV. DM is an employee of QIAGEN Ltd, a scientific advisor to Pace Diagnostics and a scientific advisor to Phoenix Solutions. RP is an employee of Shionogi Inc. JMP has served as a consultant to Merck, Shionogi, Nabriva therapeutics and QPex Pharmaceuticals. EL and LT have nothing to disclose.

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