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Clinical Studies

Nephrotoxicity prevalence in patients treated with polymyxins: a systematic review with meta-analysis of observational studies

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ABSTRACT

Colistin and polymyxin B are increasingly reintroduced in clinical practice due to the absence of effective antibiotics for the treatment of emerging infections caused by gram-negative bacteria. The synthesis of current evidence on the characteristics of polymyxins, especially regarding nephrotoxicity, is necessary. This study aims to conduct a systematic review and meta-analysis of cohort-type observational studies in order to identify the prevalence of nephrotoxicity in patients treated with either colistin or polymyxin B. PubMed, Scopus, and DOAJ electronic databases were searched, and manual searches were done. Cohort studies evaluating renal damage (nephrotoxicity) in adult patients caused by colistin or polymyxin B were included. Meta-analyses of the prevalence of nephrotoxicity as well as cumulative meta-analysis and meta-regression were conducted. After the systematic searches, 95 cohorts ($n = 7911$ patients) were included for analysis. The nephrotoxicity prevalence was 26.7% [confidence interval (CI) 95%: 22.8–30.9%] for colistin and 29.8% (CI 23.8–36.7%) for polymyxin B ($P = 0.720$). The publication year of the studies, the criteria used to classify renal damage, and the nephrotoxicity as primary or secondary outcome showed a significant influence on the adverse event rates.

1. Introduction

Polymyxins were discovered in 1947 (Storm et al., 1977), but their use was almost abandoned after many reports of acute renal injury in critically ill patients (Awdishu, 2017). However, polymyxins are being reintroduced in clinical practice due to the scarcity of effective antibiotics to treat emerging infections caused by gram-negative bacteria (Falagas and Kasiakou, 2005; Pogue et al., 2016; Rabanal et al., 2017). Among polymyxins, only colistin and polymyxin B are currently used due to their lower toxicity when compared to other drugs of the class (Falagas and Kasiakou, 2006; Kadar et al., 2013; Rabanal et al., 2017). There is no consensus on prevalence rates of nephrotoxicity in critically ill patients with studies ranging from 10% to 60% (Kassamali and Danziger, 2015; Rabanal et al., 2017; Tran et al., 2016).

Initially, nephrotoxicity was assessed only by renal function biomarker tests (creatinine or urea). Studies defined the renal damage with different measures of altered creatinine levels, such as a 50% increase, a fixed increase in mg/dL relative to baseline creatinine, or doubling initial serum creatinine (Berlana et al., 2005; Bosso and Harrison, 1991; Ouderkirk et al., 2003; Sobieszczyk et al., 2004). In 2004, Risk, Injury, Failure, Loss, End Stage Kidney Disease (RIFLE) (Bellomo et al., 2004), which defined the acute renal failure and classified renal damage based on 1.5 times the baseline creatinine value, was developed. In 2007, the Acute Kidney Injury Network (AKIN) criteria (Mehta et al., 2007) were created, considering creatinine elevation ≥0.3 mg/dL or ≥1.5 times baseline creatinine at 48-h intervals. In 2012, the Kidney Disease Improving Global Outcomes (KDIGO) classification (Khwaja, 2012) appeared, defining the acute kidney injury as a serum creatinine increase of ≥0.3 mg/dL in 48 h or ≥1.5 times the baseline creatinine in an interval of up to 7 days. These modifications in nephrotoxicity definitions should be accompanied by an update of the evidence about the studies reporting its prevalence.

Despite the importance of randomized controlled trials (RCTs) to establish evidence on a specific topic, observational studies present different results because they are performed in real-life environment and include patients with comorbidities that are usually excluded in RCTs. Observational studies evaluate factors such as adherence to treatment and long-term safety, better identifying the risks and benefits of the use of treatments in the general population, and are the most appropriate design to assess the prevalence of a particular condition (DiPietro, 2010; Verde and Ohmann, 2015).

Thus, the objective of this study was to conduct a systematic review with meta-analysis of cohort-type observational studies to identify the prevalence of nephrotoxicity in patients treated with either colistin or polymyxin B.

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2. Methods

We performed a systematic review conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (Moher et al., 2009) and Cochrane Collaboration recommendations (Higgins and Green, 2011). All steps were conducted by two independent reviewers, with a third reviewer for discrepancy resolution.

2.1. Literature selection

PubMed, Scopus, and DOAJ electronic databases were searched in September 2016, without time or language limits (see supplementary material for complete search strategy). Manual searches in the references of included studies were also performed. The studies were included if they considered the following eligibility criteria according to the PICOS model (Higgins and Green, 2011):

- Patients: individuals of any age group and clinical condition using polymyxins.
- Intervention: use of polymyxin (colistin, polymyxin B, or polymyxins—when there was no distinction between both drugs) at any dose or parenteral scheme.
- Control: studies without control group (single arm) or compared with other active treatments (antimicrobial).
- Outcomes: development of nephrotoxicity.
- Study design: analytical observational cohort studies.

Articles published in non-Roman characters, articles analyzing the association of polymyxins with other classes of antimicrobials without addressing the use of polymyxin monotherapy, studies that evaluated renal function through other renal function biomarkers other than creatinine or urea, and studies that presented results expressed in number of treatments rather than in patients were excluded.

2.2. Data extraction and quality assessment

Data extracted from the included studies were study's metadata, type of polymyxin administered, sample size, and number of patients with nephrotoxicity.

The quality assessment was performed using the New Castle Ottawa Instrument (Wells et al., 2016). This instrument evaluates the study under three main domains: selection of study groups, comparability of groups and outcome of interest, assigning specific scores to the selected items. The studies were classified according to Liu revision (Liu et al., 2015) as unsatisfactory (0–3 points), satisfactory (4 points), good quality (5–6 points), and very good quality (7–9 points).

2.3. Data analysis

Meta-analyses were performed using the Comprehensive Meta-Analysis v. 2.2, (Biostat, Englewood, NJ). For each meta-analysis, we used the random effects model and the inverse of variance method to interpolate the event rates with a 95% confidence interval (CI). The between-trial heterogeneity was estimated using the inconsistency relative index I^2 which describes the percentage of variation among studies explained by heterogeneity and not by chance. Values of I^2 above 25%, 50%, and 75% were defined as low, moderate, and high heterogeneity, respectively (Higgins and Green, 2011).

To identify the reasons for the heterogeneity and the influence of certain studies on the pooled effect size, sensitivity analyses were performed. First, hypothetical removals from individually studies were included to confirm a possible influence on the overall outcome of the meta-analyses. A meta-regression was also performed to explore a potential relationship between the publication year and nephrotoxicity. Finally, subgroup meta-analyses were performed according to the type of treatment (colistin, polymyxin B, and polymyxins in general), criteria for classifying nephrotoxicity (creatinine or urea, RIFLE, AKIN, KDIGO, or others), and study outcome (primary end-stage when the main objective of the study was to assess the renal damage or secondary end-stage when the study was not primarily aimed at assessing nephrotoxicity but performed this analysis during the course of the study). When possible, further analyses considering patient's clinical conditions, therapy dosages, and treatment duration were performed.

3. Results

A total of 361 studies were retrieved from databases after excluding duplicates. After screening of titles and abstracts, 180 were selected for full-text reading. Finally, 94 studies were selected for qualitative synthesis, and 1 additional study was included after manual search, resulting in 95 cohort studies (Fig. 1) (Akajagbor et al., 2013; Alan et al., 2014; Al-Busaidi et al., 2013; Averbuch et al., 2013; Balkan et al., 2014; Batirel et al., 2014; Berlana et al., 2005; Betrosian et al., 2008; Binh et al., 2015; Bosso and Harriso, 1991; Cagan et al., 2014; Ceylan et al., 2015; Cheng et al., 2010; Chuang et al., 2014; Collins et al., 2013; Crusio et al., 2014; Dalfino et al., 2012; Dalfino et al., 2015; de Oliveira et al., 2015; DeRyke et al., 2010; Dewan and Shoukat, 2014; Doshi et al., 2011; Dubrovskaya et al., 2013; Dubrovskaya et al., 2015; Elefritz et al., 2016; Elias et al., 2010; Falagas et al., 2005; Falagas et al., 2006; Falagas et al., 2010; Freire et al., 2014; Ganapathy et al., 2010; Garnacho-Montero et al., 2013; Gibson et al., 2016; Gul et al., 2016; Hartzell et al., 2009; Holloway et al., 2006; Hür et al., 2014; Jun et al., 2013; Kalin et al., 2012; Kalin et al., 2014; Karabay et al., 2014; Karbuz et al., 2014; Kasiakou et al., 2005; Kim et al., 2016; Koch-Weser et al., 1970; Ko et al., 2010; Koksal et al., 2016; Kubin et al., 2012; Kumar et al., 2015; Kvitko et al., 2011; Kwon et al., 2010; Kwon et al., 2014; Kwon et al., 2015; Lee et al., 2015; Leonor et al., 2013; Lim et al., 2011; Martínez et al., 2014; Mendes et al., 2009; Meza-Oviedo et al., 2015; Montero et al., 2009; Mostardeiro et al., 2013; Nandha et al., 2013; Nazer et al., 2015; Nelson et al., 2015; Oliveira et al., 2008; Oliveira et al., 2009; Omrani et al., 2015; Ouderkirk et al., 2003; Paul et al., 2010; Petrosillo et al., 2014; Phe et al., 2014; Pintado et al., 2008; Pogue et al., 2011; Polat et al., 2015; Porwal et al., 2014; Rigatto et al., 2016; Rios et al., 2007; Rocco et al., 2013; Rodriguez et al., 1970; Santamaría et al., 2009; Sekhri et al., 2013; Siddiqui et al., 2014; Sobieszczyk et al., 2004; Sorlí et al., 2013; Tanita et al., 2013; Temocin et al., 2015; Thamlikitkul and Popum, 2016; Tigen et al., 2013; Tigen et al., 2016; Trifi et al., 2015; Tuon et al., 2014; Vicari et al., 2013; Yilmaz et al., 2013; Yilmaz et al., 2015; Zalts et al., 2016). The 95 studies were also included in the quantitative analyses, but 5 studies performed a direct comparison between colistin and polymyxin B, and subsequently, the 2 arms were included, resulting in 100 cohorts meta-analyzed. These studies were published between 1970 and 2016, comprising a population of 7911 patients. Most studies were conducted in the United States ($n = 21$, 22.1%) followed by Turkey ($n = 18$, 18.9%) and Brazil ($n = 11$, 11.6%). Colistin was reported in 76 studies and polymyxin B in 19. Most cohorts are retrospective (81%) (Supplementary Material).

The methodological quality of the studies was generally considered satisfactory (13.7% very good, 14.7%, good 54.7% satisfactory, and 16.8% unsatisfactory) (Supplementary Material). Most of the cohorts were composed by specific groups of patients (94.7%), with only 1 arm (without an unexposed comparator group) (83.2%). The author did not demonstrate that the outcome of interest was not present at the beginning of the study in 89.5% of the articles, and the majority (81%) used patients' medical records as source of information. The cohort follow-up was greater than 30 days in all the analyzed studies, with around 98% of studies reporting complete follow-up information for all patients.

Overall prevalence of nephrotoxicity was 27.5% (95% CI: 24.3–30.9%), ranging from 0 to 76.1% with high heterogeneity ($I^2 = 88.903$; $P < 0.001$) (Fig. 2). Sensitivity analysis excluding 1 study at a time could not identify any study as responsible of this high heterogeneity (Supplementary Material). The subgroups analyses showed no

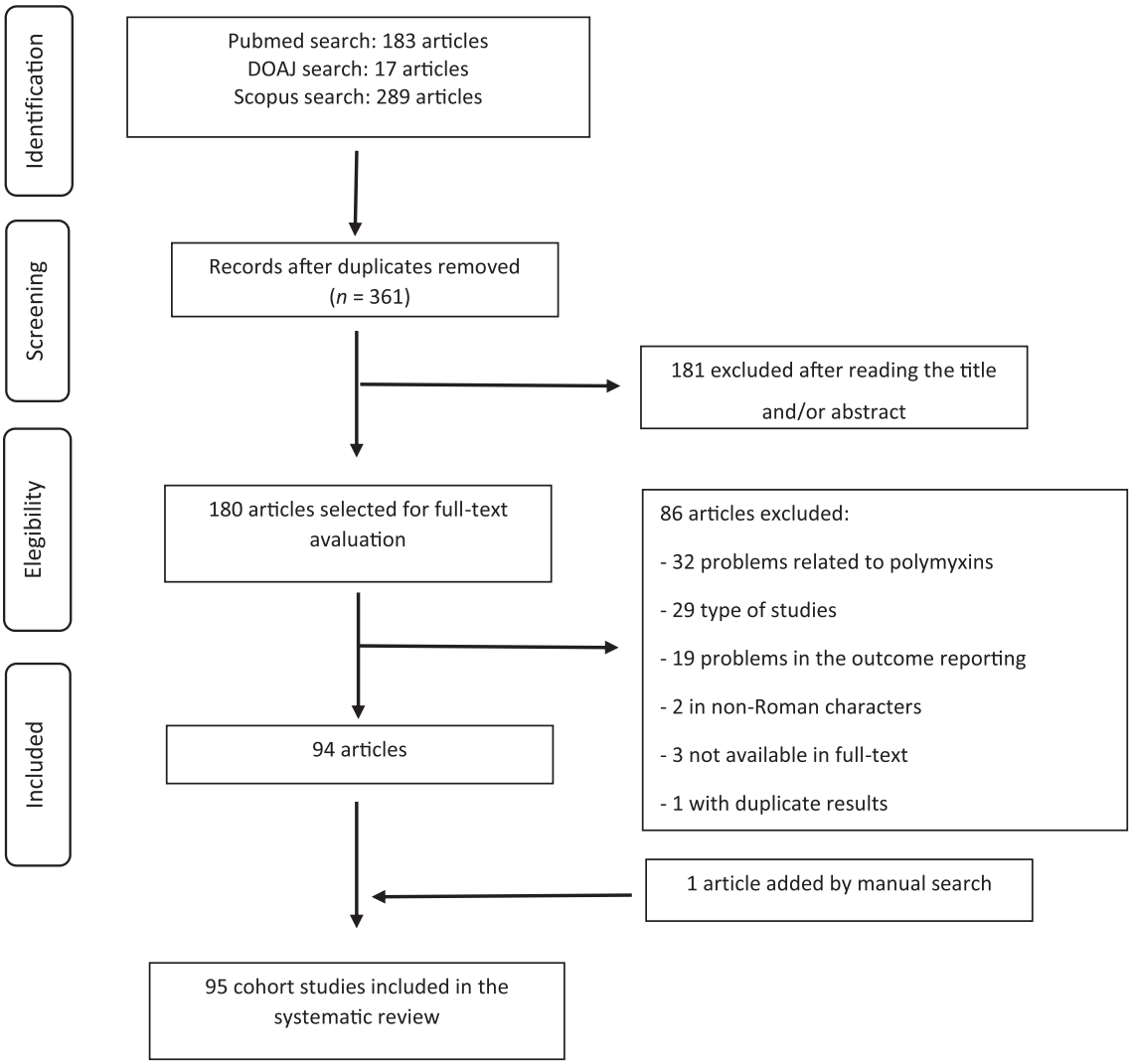

Fig. 1. Flow diagram of the article selection process

differences ($P = 0.720$) between the prevalence of nephrotoxicity for colistin [26.7% (CI of 22.8–30.9%, $I^2 = 89.603$)], polymyxin B [29.8% (CI 23.8–36.7%, $I^2 = 87.201$)], and polymyxins in general [27.7% (IC 18.3–39.6%, $I^2 = 74.659$)] (Fig. 3). Similarly, no differences between colistin and polymyxin B were found when considering only studies that classified nephrotoxicity using internationally recognized criteria (RIFLE, AKIN, or KDIGO) [37.8% (CI of 33.5–42.3%, $I^2 = 84.473$) and 38.5% (CI of 30.7–46.9%, $I^2 = 85.992$) respectively ($P = 0.880$)] (see Supplementary Material).

The cumulative meta-analysis (Supplementary Material) showed that the prevalence of nephrotoxicity significantly increased over the years. In the 1970s, the rates reported for this event were around 2%, with a gradual increase, reaching 26% in 2015 and 27% in 2016. The meta-regression confirmed that the publication year was directly correlated to the prevalence rate of nephrotoxicity (slope 0.06471). With the removal of the 11 studies published before 2007, the prevalence of nephrotoxicity increased to 30.3% (CI 26.9–33.8%, $P < 0.001$) (Fig. 4).

Criteria used to define renal damage resulted in different prevalence of nephrotoxicity ($P < 0.001$). The 42 studies using creatinine or urea levels resulted in a prevalence of 14.3% (CI 10.6–19.0), the 46 studies using RIFLE resulted in 39.4% (CI 35.2–43.7), the 9 studies using AKIN resulted in 32.6% (CI 25.5–40.7), and the 2 studies using KDIGO resulted in a prevalence of 31.3% (CI 24.2–39.4). One article did not report how renal damage was identified, with the prevalence of the event being 17.6% (CI 5.8–42.7) (Fig. 5). A difference ($P = 0.002$) was also identified between the studies that considered nephrotoxicity as the primary outcome (event rate 30.9% [CI 27.2–34.9%]) and those considering it as secondary outcome (17.6% [CI 12.1–24.9]) (Fig. 6).

Further analyses considering patient's clinical conditions (critically ill versus not critically ill patients), therapy dosages, and treatment duration were hampered given the lack of studies properly reporting data or due to data heterogeneity (e.g., therapy doses expressed in different units: different times of exposure to the risk among patients expressed as median or means).

4. Discussion

This study is the first to gather evidence from 95 cohort studies on the prevalence of nephrotoxicity associated with the use of polymyxins over the years. The methodological quality of these real-life studies was considered satisfactory and sufficient to generate evidence of polymyxins use in critically ill patients. However, attention should be paid to the high heterogeneity among studies, evidenced in some of our meta-analyses. This heterogeneity was probably caused by a combination factors including lack of comparator group (unexposed) in the cohorts, small sample size of some studies, variability among patients (baseline characteristics and clinical conditions), and the variations in the interventions being assessed, as well as in the measurement of

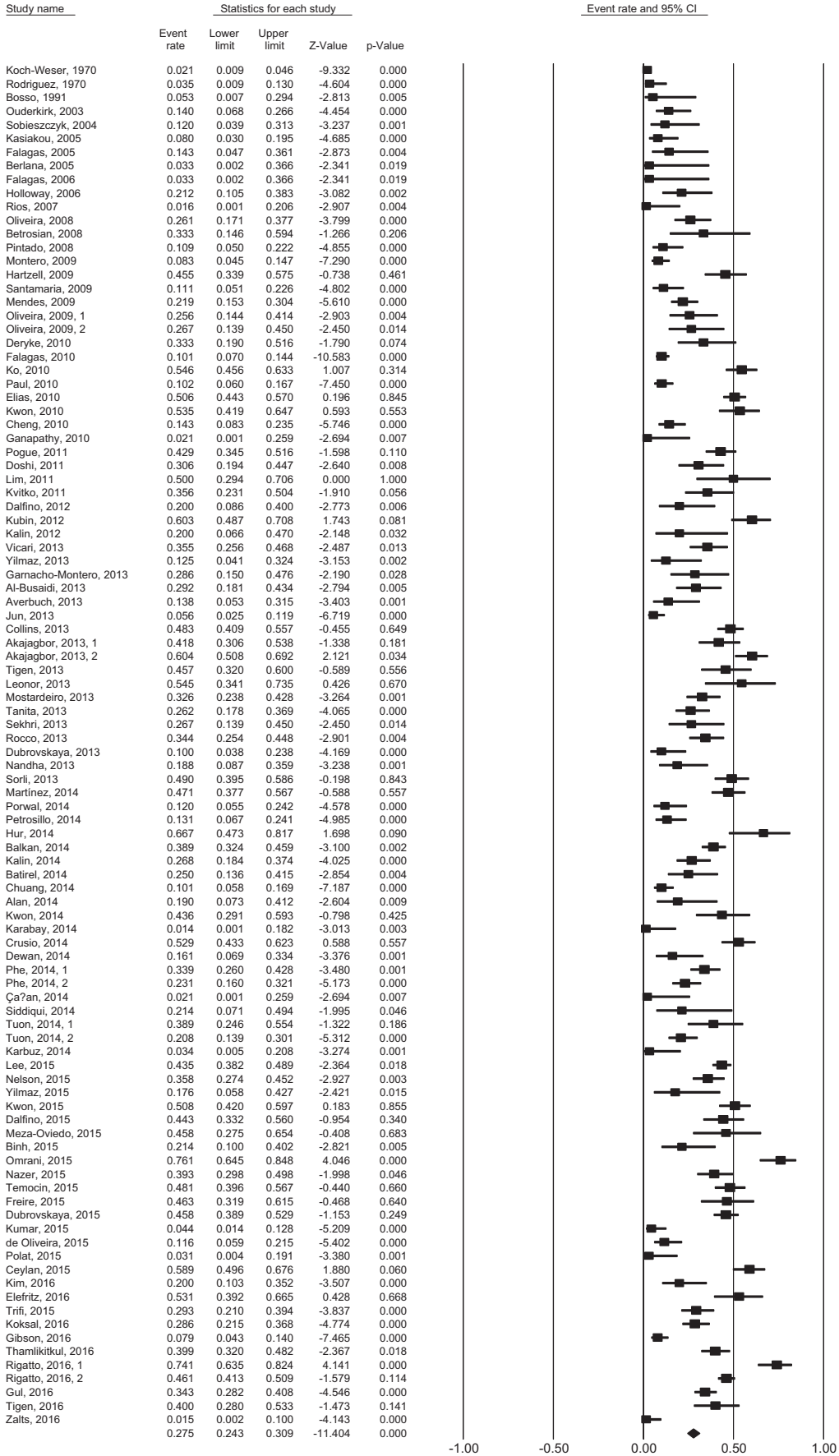

Fig. 2. General prevalence of nephrotoxicity in patients treated with polymyxins.

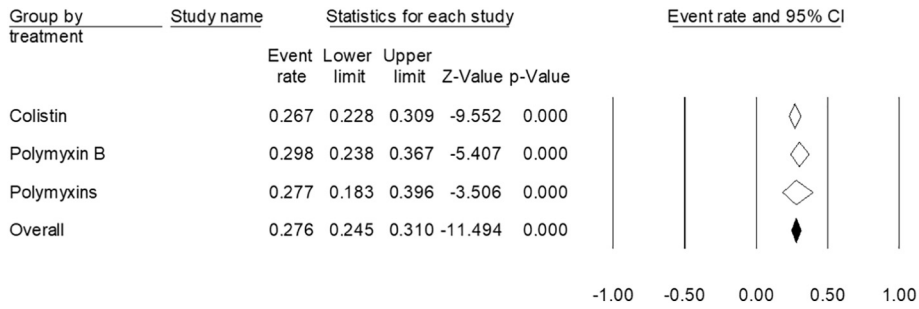

Fig. 3. Meta-analysis according to subgroups of treatments.

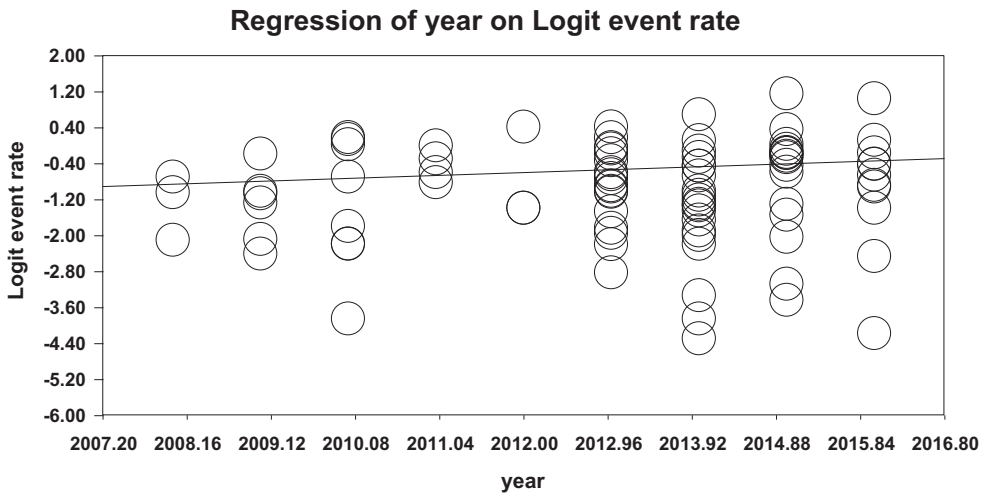

Fig. 4. Meta-regression of the year of publication in relation to nephrotoxicity.

outcomes. Nonetheless, when compared to randomized clinical trials, high heterogeneity values are much more common and acceptable for observational studies (Higgins and Green, 2011; Higgins and Thompson, 2002).

The overall meta-analysis of the nephrotoxicity prevalence presented rates close to 30% but with high variability and gradual increase over the years. In addition to the differences in baseline and clinical characteristics of patients, which are known to impact on the prevalence of adverse events (Kassamali and Danziger, 2015), our meta-regression demonstrated that the year of publication of the studies had a direct and significant influence on the results. Studies published before 2007 have shown significantly lower rates. This is probably due to the changes in the thresholds for renal function over the years. Studies published until 2008 used only serum creatinine dosages to assess renal damage (Berlana et al., 2005; Betrosian et al., 2008; Bosso and Harrison, 1991; Falagas et al., 2005, 2006; Holloway et al., 2006; Kasiakou et al., 2005; Koch-Weser et al., 1970; Oliveira et al., 2008; Ouderkirk et al., 2003; Pintado et al., 2008; Rios et al., 2007; Rodriguez et al., 1970; Sobieszczyk et al., 2004). The Hartzell study (Hartzell et al., 2009) used for the first time, in 2009, the RIFLE criteria for the assessment of nephrotoxicity associated with the use of polymyxins. Hereafter, other studies started to use RIFLE and other internationally recognized criteria such AKIN and KDIGO. This significantly altered the sensitivity of renal damage detection when compared to studies reporting only serum creatinine, with an annual increase of approximately 6% in the nephrotoxicity rates. Among studies using standardized international criteria, the results for nephrotoxicity rates were similar, probably because the parameters to detect renal damage

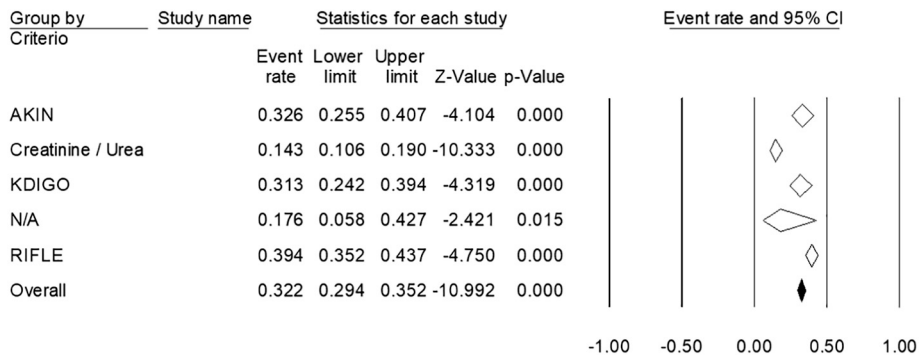

Fig. 5. Meta-analysis of subgroups according to the criteria used to classify nephrotoxicity.

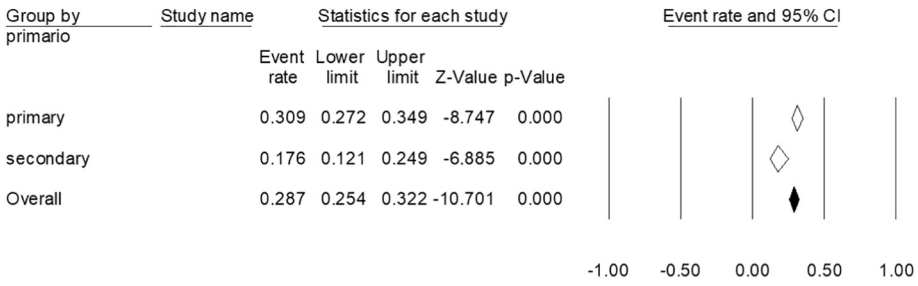

Fig. 6. Meta-analysis of subgroups according to the nephrotoxicity outcome of the study.

resemble. RIFLE presented the highest value for prevalence of nephrotoxicity, probably because more studies used this criteria ($n = 46$) when compared to other (AKIN $n = 9$ and KDIGO $n = 2$).

Another factor that may have significantly influenced and underestimated some results is how the outcome was reported in the studies. We found that in studies where nephrotoxicity was considered as secondary outcome, rates of renal damage were one third lower than those where nephrotoxicity was the primary outcome. Secondary outcomes are usually associated with significantly reduced severity during their definition and report in the study, which may influence the detection rates when compared to the assessment of primary outcomes. This inadequate reporting affects the quality of the study and can lead to biased outcomes and misinterpretations (Mantziari and Demartines, 2017; Matthews et al., 2016). Compliance with recommendations for conduction and reporting of observational studies such as Strengthening the Reporting of Observational Studies in Epidemiology (von Elm et al., 2007) should be followed by the authors and required by reviewers and editors before the publication of the studies.

The nephrotoxicity rates found in our study were similar for both evaluated drugs (colistin and polymyxin B). These data confirm the review by Kassamali and Danziger (2015), which concludes that both drugs are appropriate for clinical use. However, in a meta-analysis of 5 head-to-head studies published by Vardakas and Falagas (2017), the authors stated that patients treated with colistin are more likely to develop treatment-related nephrotoxicity (Akajagbor et al., 2013; Oliveira et al., 2009; Phe et al., 2014; Rigatto et al., 2016; Tuon et al., 2014). In our systematic review and meta-analyses, besides these 5 head-to-head studies, we included a higher number of cohorts (76 for colistin and 19 for polymyxin B), which significantly increase the statistical power of the results and reduce possible biases. We finally found that no significant difference among therapies for nephrotoxicity exists.

Colistin has a bigger availability in the world market when compared to polymyxin, which may favor the high number of studies with this drug (Kassamali and Danziger, 2015; Nation et al., 2015). However, due to the increased need for alternatives to treat emerging infections and improve the existing therapies, studies discuss spreading the use of polymyxin B (Zavascki and Nation, 2017), especially because mortality associated with this drug demonstrated to be similar to colistin (without significant differences) (Vardakas and Falagas, 2017). Kassamali and Danziger (2015) question the replacement of colistin with polymyxin B, while authors such as Rabanal et al. (2017) offer prospects in the development of new polymyxins with the goal of improving activity and minimizing nephrotoxicity. Considering drug's dosage, subgroup analyses were not possible given the high heterogeneity of reported data of primary studies. Usually, the dose of polymyxin B (intravenously) is calculated according to the patient's body weight, which can vary from 15,000 to 25,000 U/kg/d and should not exceed the maximum of 25,000 U/kg/d. For colistin, considering colistimethate sodium (CMS) as the pharmaceutical product, the dose to treat infections caused by gram-negative bacteria is 2.5 to 5 mg/kg/d, usually divided into 2 to 4 times per day (Greenwood Village, 2018). Both CMS and polymyxin B are filtered in the glomerulus, but only CMS is significantly eliminated by the kidney, suggesting that the doses of this drug should be adjusted in patients with decreased renal function in order to prevent overexposure to colistin. However, because colistin and polymyxin B are highly resorbed by the body, being eliminated by other nonrenal pathway, no dose adjustments are usually necessary (Pogue et al., 2017).

The reintroduction of polymyxin in clinical practice should consider the overall therapeutic effect of both drugs tailored to each clinical and economic scenario. In addition, there is a need for more detailed guidelines to conduct and report nephrotoxicity in clinical trials and observational studies in order to standardize and more accurately estimate the occurrence of this adverse reaction. The use of international criteria such as RIFLE, AKIN, and KDIGO for the evaluation of nephrotoxicity is essential for studies in this area and should be requested by editors and reviewers.

Our study has some limitations. Given the lack of standardized report in primary studies, criteria for extracting kidney damage data were necessary. We used the term “nephrotoxicity” because it is the most comprehensive. Nephrotoxicity was evaluated as an outcome of interest for this systematic review because it is the main adverse event of polymyxins, but other events should be studied. We analyzed only observational studies because they represent a sufficiently good level of evidence for prevalence assessment considering real-world settings. The low reporting quality of some studies (e.g., lack of raw data such as precision estimates — standard error, confidence interval) and variance between results hampered more analyses to be performed.

5. Conclusion

Both colistin and polymyxin B showed a similar profile for the occurrence of renal damage with about 27% in critically ill patients. Prevalence rates increased through the years in studies with nephrotoxicity as a primary outcome and with the use of standardized international renal damage criteria (i.e., RIFLE, AKIN, KDIGO). The use of these renal damage criteria and reporting guidelines for observational studies (i.e. Strengthening the Reporting of Observational Studies in Epidemiology) should be enforced by editors and peer-reviewers.

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Conflict of interest

There is no conflict of interest.

Ethical approval

Not required.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diagmicrobio.2018.11.008.

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