# Meta-analysis of Polymyxin Use in Patients

11

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**Abstract**

In this chapter, we systematically reviewed studies that assessed polymyxin's effectiveness and summarized results through meta-analysis. The outcomes addressed were all-cause mortality, assuming that for patients with severe multidrug-resistant infections survival is the most important outcome, and resistance development, important for future patients. Most clinical data on polymyxins in the literature are from retrospective, observational studies at high risk of bias. The majority of clinical studies were unpowered to examine mortality controlling for other risk factors. The studies had no control of dosage regimens and treatment modifications. We identified several areas of missing data, in particular randomized controlled trials (RCTs) examining treatment options for carbapenem-resistant Gram-negative bacteria, different dosage regimens, polymyxins versus alternative antibiotics (e.g. aminoglycosides, tigecycline), and monotherapy versus specific combination therapies. Ideally, mortality and development of resistance should be examined in RCTs, with further longitudinal studies required for the latter.

**Keywords**

Meta-analysis · Polymyxin · Randomized controlled trial · Resistance · Combination therapy

## 11.1 Why Focus on Meta-analysis

Meta-analysis is a statistical technique of combining results from different studies. In itself the term conveys little information on the methodology of a study, as the selection criteria for the studies combined are crucial to the meta-analysis results. Systematic reviews define precisely the question addressed and the studies to be included in a meta-analysis and then attempt to include each and every study that has been performed. The advantage over a narrative review is that the information contained within the summary result is transparent and highly specific. This is also the limitation of the meta-analysis result; it addresses precisely the question addressed (patient population, intervention, comparison and outcome).

Meta-analysis provides a single point estimate summarizing all known studies that is much

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simpler to deal with than the many separate results of the original individual studies. However, many times the pooled estimate has poor credibility because of heterogeneity in the patient populations, interventions and outcomes assessed despite the attempt to ask specific questions. For example, addressing the question of the survival benefit of colistin-meropenem combination therapy vs. colistin monotherapy among patients with bloodstream infections is seemingly highly specific. However, the studies might evaluate mortality at different time points (in-hospital, 14-day, 28-day), colistin and meropenem might be given in different doses and schedules, patients might be infected by different Gram-negative bacteria with different MICs for meropenem. Readers of meta-analyses are advised to critically examine whether the pooled effect estimate is useful. Frequently meta-analyses will examine clinical and statistical heterogeneity and might be able to point to the factors underlying differences in results.

In this chapter, we will address systematically several questions previously reviewed in the book and try to summarize results through meta-analysis.

## 11.2 "Effectiveness"

The only study design appropriate to examine the effectiveness of a drug is a well-powered and well-conducted randomized controlled trial (RCT), since only RCTs can achieve unbiased comparisons. There are no RCTs comparing colistin vs. another antibiotic for the treatment of severe infections. Historically, colistin has been considered as poorly effective and has been replaced by beta-lactams once broad-spectrum beta-lactams covering Gram-negative bacteria became available. Currently several studies and authors claim that colistin is "effective". Its use has certainly increased in recent years and it is a primary mode of treatment for carbapenem-resistant bacteria. The question of effectiveness is important as it should determine our inclination to use colistin empirically, before we know whether the patient is infected with carbapenem-resistant bacteria. It should also determine the selection of the antibiotic to be used against carbapenem-resistant bacteria if the isolates are susceptible in-vitro to antibiotics other than colistin (e.g. an aminoglycoside, fosfomycin, tigecycline). Contained within the question of the effectiveness of colistin is also the question of optimal dosing.

Given the lack of RCTs, we compared contemporary observational studies that assessed the effectiveness of colistin (update of a previous review [1]). The inclusion criteria were studies comparing a systemic polymyxin against a drug regimen not including a polymyxin in a comparative clinical trial, cohort (prospective or retrospective) or case-control design and reporting on mortality. We did not restrict inclusion by type of infection or bacteria.

Three studies permitted a comparison between patients given colistin vs. patients receiving inappropriate antibiotic treatment (empirical treatment) [2–4]. Mortality was higher with inappropriate antibiotics, with heterogeneity between the studies (Fig. 11.1). Adjusted analyses were not available.

Thirteen studies compared polymyxins to another antibiotic [5–17]. All studies examined patients with severe healthcare-associated infections (most commonly pneumonia and bacteremia) caused by highly-resistant bacteria. *Acinetobacter baumannii* and *Pseudomonas aeruginosa* were the common bacteria and *Klebsiella pneumoniae* was more rarely assessed. Polymyxins (colistin in all but two studies) were given to patients with carbapenemase-producing or phenotypically carbapenem-resistant Gram-negative bacteria (CRGNB). Colistin was used as monotherapy in a single study [14] and in the other studies polymyxins were most commonly given in combination with other antibiotics. The comparator arm included patients with multidrug-resistant (MDR) bacteria susceptible to the non-polymyxin comparator drug and that were treated with beta-lactams (most commonly carbapenems), tobramycin (one study [8]) or tigecycline (one study [11]). Individual study results and the pooled summary for all-cause mortality are presented in Fig. 11.2. The pooled unadjusted result

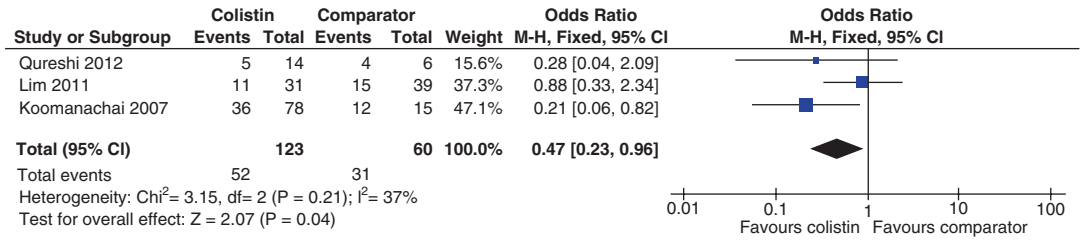


**Fig. 11.1** Mortality for patients treated with colistin vs. inappropriate antibiotics

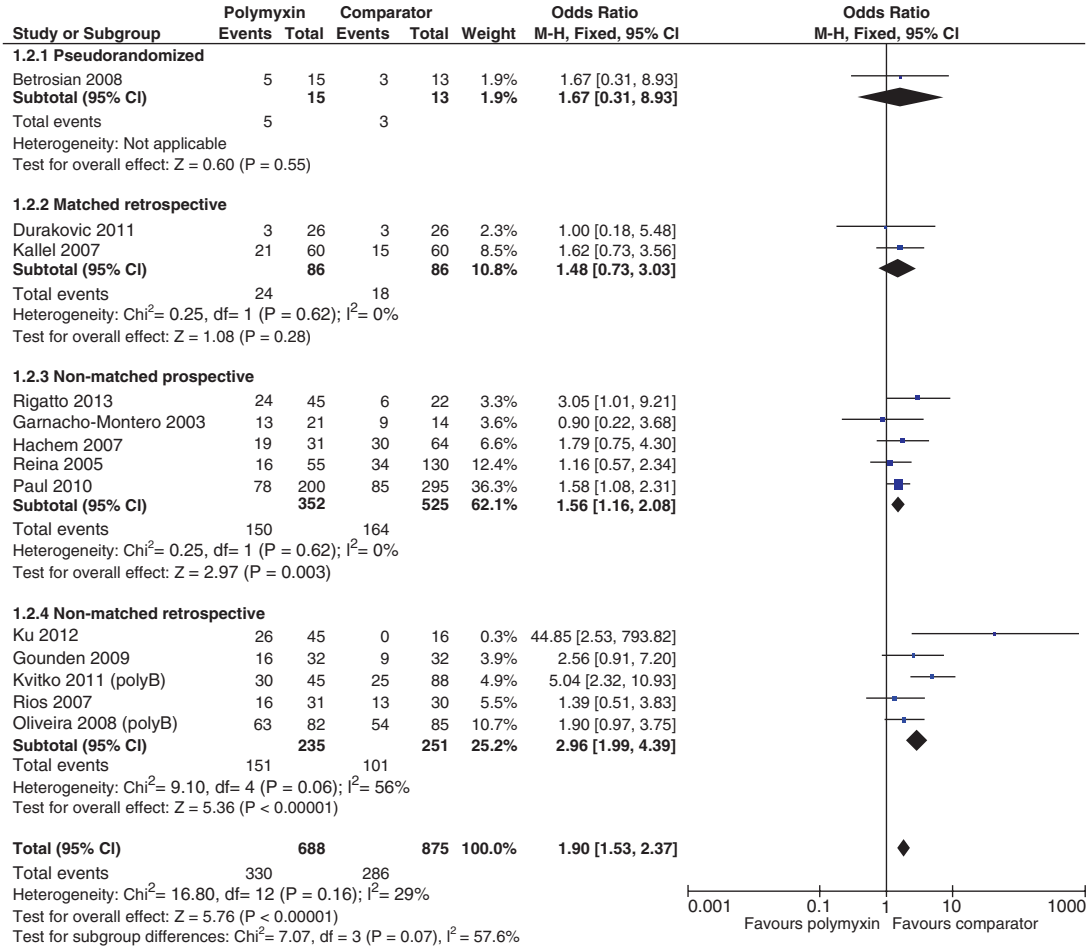


**Fig. 11.2** All-cause mortality for polymyxin vs. comparator antibiotics, unadjusted results

showed nearly twice the mortality odds with polymyxins compared to comparator drugs. The study design affected results: the meta-analysis forest plot is subcategorized by study design, from the least risk of bias (top) to the highest (bottom) and odds ratios increase from top to bottom. However, a meta-analysis of adjusted odds ratios (ORs) or odds ratios from studies using matching shows also significantly higher mortality with polymyxins with no statistical heterogeneity (adjusted OR 1.79, 95% confidence intervals (CI) 1.35–2.36, Fig. 11.3). Assessment

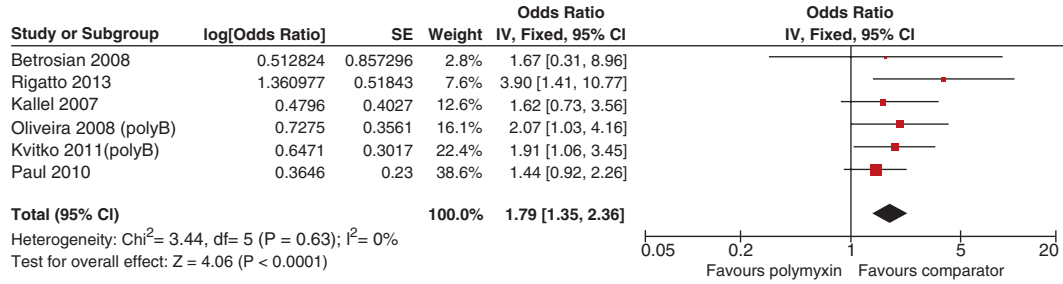


**Fig. 11.3** All-cause mortality for polymyxin vs. comparator antibiotics, adjusted results

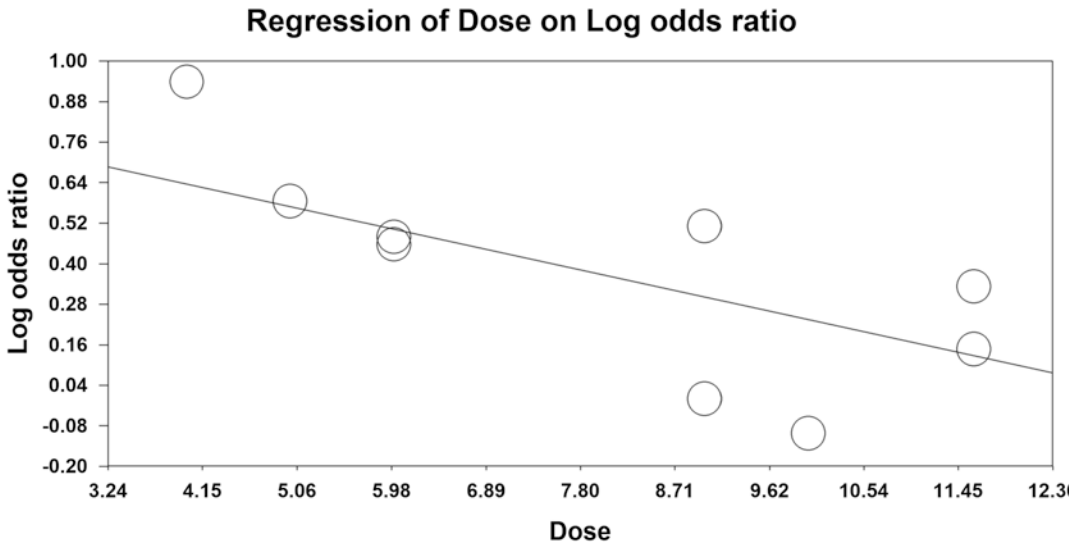


**Fig. 11.4** Meta-regression of unadjusted ORs for mortality with mean colistin dose in study
Colistin dose given in million international units (MIU). P for slope = 0.21

of the effect of colistin dose on results was possible in univariate analysis only including 9 studies that reported the mean colistin dose used. The meta-regression is shown in Fig. 11.4; although, not statistically significant, a trend is shown of increasing ORs (greater advantage to comparator arm) with lower colistin dosing (presented in million IUs).

Thus, the compilation of existing studies shows that polymyxins may be more effective than no antibiotics and less effective than beta-lactams. The comparison to antibiotics potentially active against CRGNB is limited to single studies. This is based on observational studies with major limitations, of which the main is that different patients are compared. Those treated with colistin have infections caused by CRGNB while those treated with comparator antibiotics usually had carbapenem-susceptible bacteria. Therefore, these studies do not assess the effectiveness of colistin (hence "effectiveness"), but its association with mortality with many limitations. Polymyxins were administered in combination, thus results are relevant to colistin combination therapy. Colistin was given in some of the studies at a lower dose than currently recommended [18, 19] and without a loading dose and lower dosing might have been associated with a larger advantage to comparator drugs. Few retrospective studies compared colistin to polymyxin B [20–23]; the cohorts were too different to allow reasonable comparisons between groups

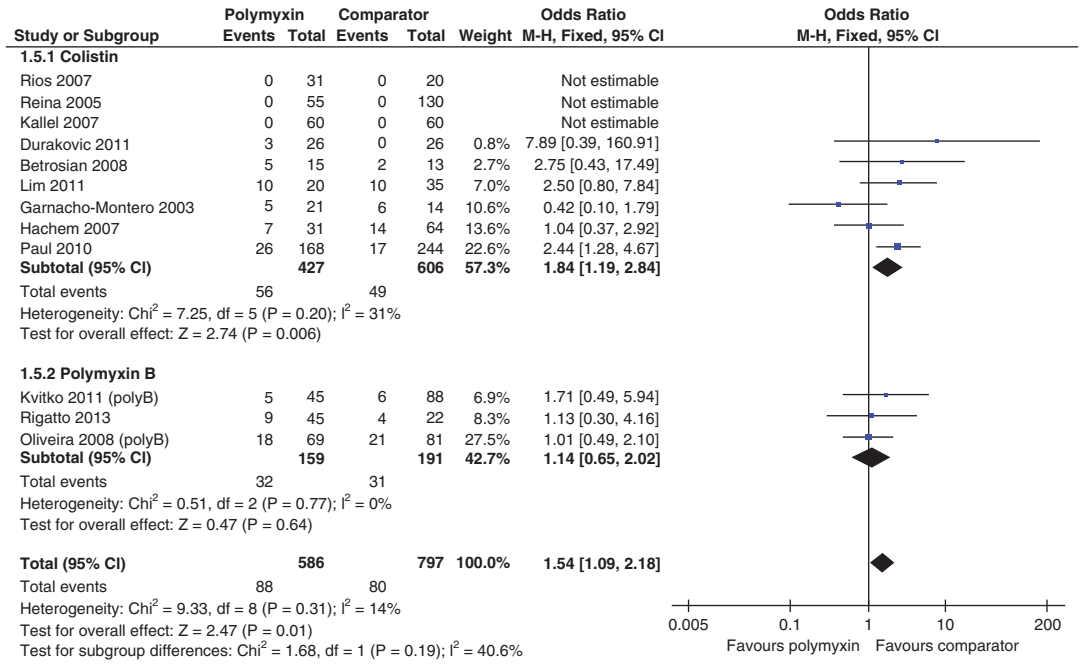


**Fig. 11.5** Nephrotoxicity with polymyxins vs. comparator antibiotics, unadjusted results

for mortality and adjusted analyses for mortality were not conducted.

## 11.3 Nephrotoxicity

The same studies allowed the assessment of nephrotoxicity rates with polymyxins vs. non-polymyxins [3, 5–7, 9, 10, 12–17]. Nephrotoxicity was most commonly defined as at least a 1.5–2 fold increase in serum creatinine from baseline (RIFLE "risk" and above [24]). Ten studies examining colistin were identified, showing higher nephrotoxicity rates with colistin vs. comparator antibiotics, unadjusted OR 1.75 (95% CI 1.16–2.64, Fig. 11.5). Two studies examining polymyxin B did not show a significant difference vs. comparators (Fig. 11.5). None compared a polymyxin to an aminoglycoside.

Recent studies claim higher nephrotoxicity rates with colistin compared to polymyxin B [20–23]. In these studies, selection of patients depended on the type of polymyxin available (comparison between time periods or hospitals). All studies were retrospective and nephrotoxicity was similarly defined as RIFLE "risk" and above [24]. We pooled adjusted odds ratios or odds ratio reported from matched patient cohorts (non-significant univariate results taken from one study). Overall, the nephrotoxicity rate was observed to be about two-fold higher with colistin compared with polymyxin B, adjusted OR 2.12 (95% CI 1.46–3.07, Fig. 11.6).

## 11.4 Combination Therapy

Currently much debate surrounds the issue of polymyxin combination therapy. Empirical combination therapy is reasonable given that polymyxins are less effective than other antibiotics but more effective than no antibiotics, as shown above. The issue of debate regards combination therapy for CRGNB after receipt of the final pathogen identification and susceptibility results. Some would consider the question also pertinent for carbapenemase-producing Gram-negative bacteria that are phenotypically susceptible to carbapenems. The answer probably depends on the precise MIC of the isolate and perhaps on the type of bacterium.

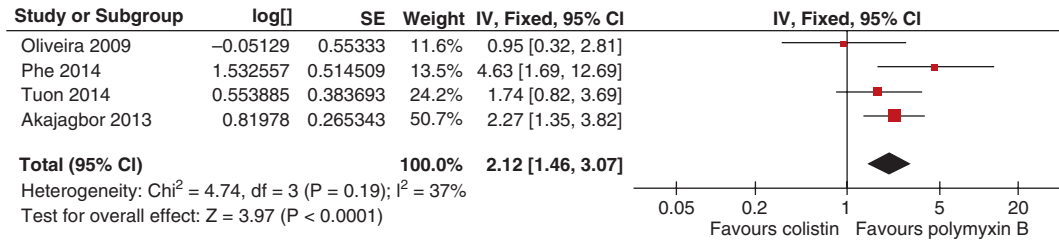


**Fig. 11.6** Nephrotoxicity with colistin vs. polymyxin B, adjusted analysis

The rationale for combination therapy is based on synergy, enhanced bactericidality and prevention of polymyxin-resistance development. In a systematic review and meta-analysis we analysed in-vitro interactions between polymyxins and carabapenems for different Gram-negative bacteria [25]. Synergy rates for different carbapenems and different bacteria ranged between 24% (meropenem for *P. aeruginosa*) to 88% (doripenem for *A. baumannii*). Among all carbapenem-polymyxin combinations, synergy rates were highest for *A. baumannii*. Among all bacteria, doripenem achieved highest synergy rates with polymyxins. Antagonism rates were low; the highest value, 24%, was observed for imipenem-polymyxin against *K. pneumoniae.* Bactericidal activity of the combination was greater than that of the polymyxins in most assays, increasing from 10–26% with the polymyxin to 49–74% in different isolates. Resistance developed rapidly with polymyxins alone, whereas the combination therapy generally suppressed and delayed resistance development.

While the in-vitro data appear promising, clinical results might be very different from in-vitro interactions. We compiled all clinical studies comparing colistin administered as monotherapy vs. combination therapy including colistin for the treatment of CRGNB or carbapenemase-producing Gram-negative bacteria [26]. We included RCTs and observational studies. When the same patients were included in more than one publication, we included the publication describing the largest number of patients. The outcome assessed was all-cause mortality. Results are summarized in Fig. 11.7.

Two RCTs compared colistin alone vs. colistin-rifampin for infections caused by *A. baumannii* [27, 28], showing no survival advantage to the combination arm. In both an advantage to colistin-rifampin was shown for secondary outcomes; clinical or microbiological cure. One RCT compared colistin alone vs. colistin-meropenem combination therapy, both administered with optimized high dosing [29]. All other studies were observational (all but two retrospective) ranging from very small case series to cohort studies, the largest analysing 250 patients. Nine studies permitted the comparison between colistin alone vs. colistin-carbapenem combination therapy [4, 29–36]. No advantage was observed to combination therapy OR 0.97, 95% CI 0.69–1.35, unadjusted except for the results of the single RCT). Similarly, the comparisons between colistin monotherapy vs. colistin combined with tigecycline, sulbactam and aminoglycoside showed no significant difference between regimens [4, 11, 30, 32, 34, 37, 38]. Four studies presented a comparison between colistin monotherapy vs. "any" combination therapy, that is difficult to translate to clinical practice. Combinations frequently included three-drug regimens. In this set of studies the combination therapy was significantly associated with higher mortality (unadjusted OR 2.09, 95% CI 1.33–3.28). The risk of bias in these studies was very high, as previously discussed [26]. The main reason underlying heterogeneity in the observational studies was carbapenem MICs, with lower MICs associated with an advantage to the combination therapy.

Thus, these meta-analyses show that despite favorable in-vitro interactions for specific antibiotic combinations, clinical studies do not demonstrate an advantage to combination therapy. The only combinations that have been tested in RCTs are those of colistin-rifampin and colistin-

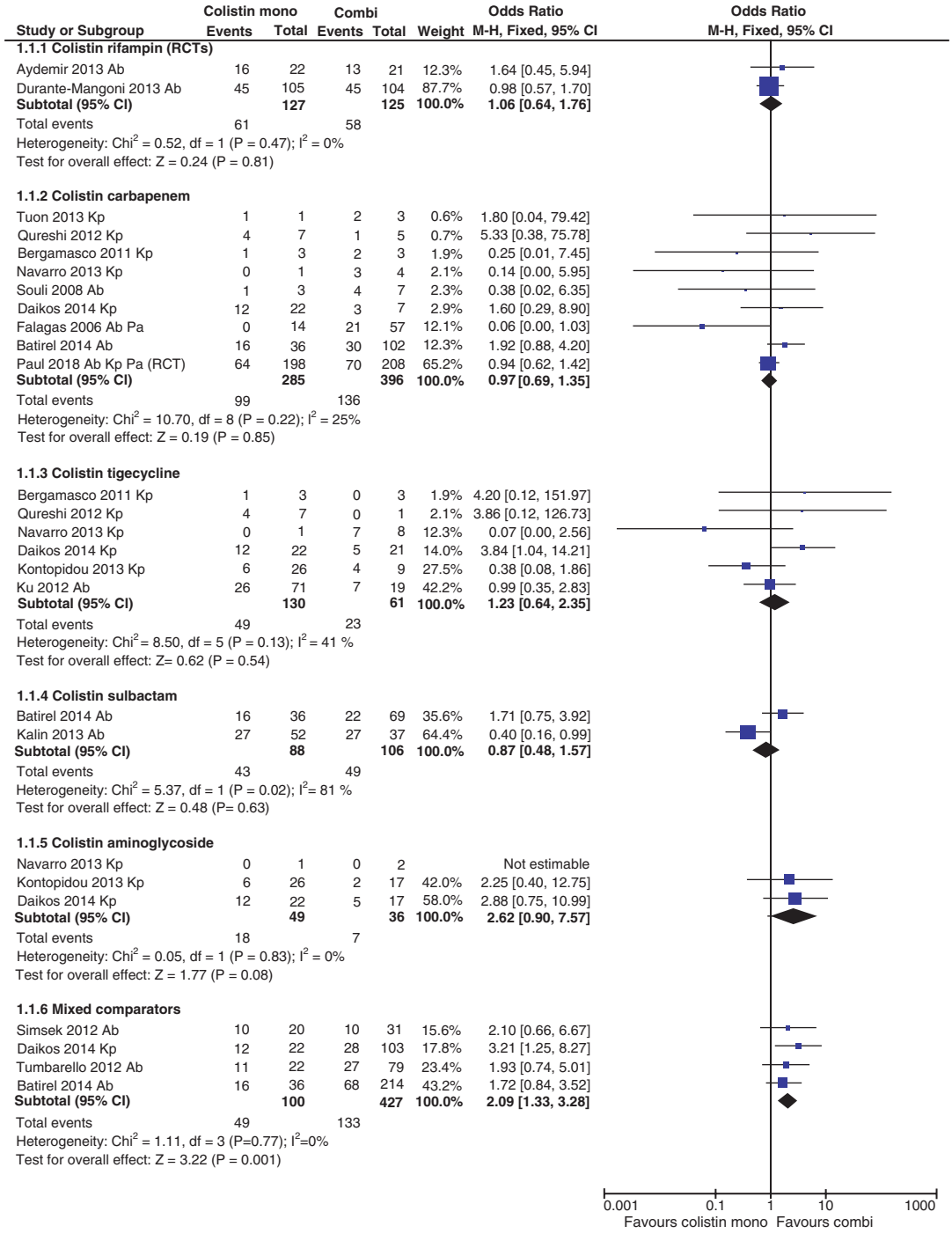


**Fig. 11.7** All-cause mortality for colistin monotherapy vs. colistin combination therapy, unadjusted results

meropenem, and the results of the RCTs do not justify the use of this combination. Critical assessment of the observational studies shows very serious risk of bias and no significant survival advantage to specific polymyxin combinations. Lacking support for combination therapy for CRGNB, we believe that this practice should not be adopted as the routine. The discrepancy

between in-vitro and clinical studies calls for well-conducted RCTs to examine specific antibiotic combinations. Such trials are under way and will determine future clinical practice.

## 11.5 Colistin Inhalation Therapy

Since polymyxins penetration into lung tissue is poor, nebulized colistin is sometimes being used for the treatment of respiratory tract infections. We searched for RCTs, cohort (prospective or retrospective) and case control studies comparing colistin administered as inhalation/nebulized therapy alone or with systemic treatment vs. systemic only antibiotic treatment in the treatment of ventilator-associated pneumonia or nosocomial pneumonia caused by MDR Gram-negative bacteria. We excluded studies examining patients with cystic fibrosis.

Three studies compared colistin inhalation alone vs. systemic antibiotic treatment for the treatment of pneumonia caused by *A. baumannii* or *P. aeruginosa* (one in neonates) [39–41]. None used matching nor reported on adjusted mortality rates. All-cause mortality was significantly lower among patients receiving colistin inhalation therapy alone compared to those treated with systemic treatment, usually polymyxins (unadjusted OR 0.37, 95% CI 0.17–0.82), with significant heterogeneity in results (Fig. 11.8).

Seven studies assessed the use of colistin inhalation as adjunctive therapy to systemic antibiotics for the treatment of *A. baumannii* (most commonly), *P. aeruginosa* or *K. pneumoniae*. One was a RCT [42], two used matching criteria for patients given colistin inhalations and those treated with systemic antibiotics alone [43, 44] and the remaining were unmatched and did not report an adjusted analysis for mortality [40, 45, 47]. The RCT showed no difference in mortality between study arms, while the observational studies showed a trend in favor of the adjunctive colistin inhalations, with heterogeneity in results (overall pooled OR 0.76, 95% CI 0.54–1.05, Fig. 11.9). A main concern with colistin inhalations is the induction of polymyxin-resistant bacteria, but the studies did not report on comparative resistance development rates. As expected, these studies show higher rates of eradication of the MDR bacteria from the respiratory tract with colistin inhalations.

These studies are suggestive of a possible benefit for colistin inhalation therapy, but these cannot form a basis for treatment recommendations. Selection bias is likely present in the analysis assessing colistin inhalations alone and this and other sources of bias affect the analysis of adjunctive colistin inhalations. The only RCT showed no advantage regarding survival for adjunctive colistin inhalations. Given the positive results of the observational studies, further RCTs are warranted and further observational studies should assess the long-term effects of colistin inhalations on the emergence of resistance.

## 11.6 Summary

Meta-analysis is an elegant tool to summarize outcome data gained from RCTs. Much of the data on polymyxins to date is based on observational studies at high risk of bias. The studies were unpowered to examine mortality, adjusting for all known

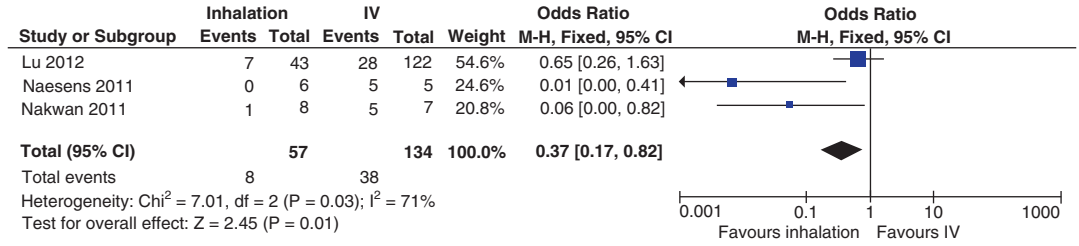


**Fig. 11.8** All-cause mortality for colistin inhalations alone vs. systemic antibiotics in the treatment of pneumonia

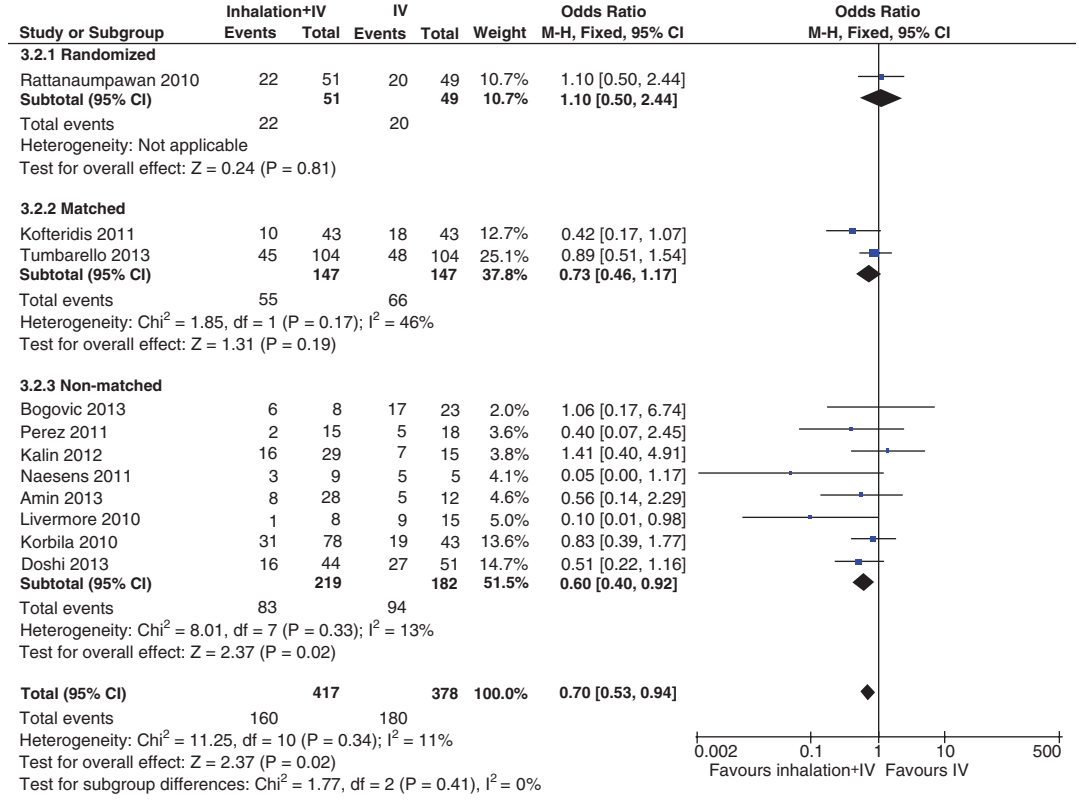


**Fig. 11.9** All-cause mortality for colistin inhalations combined with systemic antibiotics vs. systemic antibiotics in the treatment of pneumonia

risk factors for mortality. Most studies were retrospective and had no control of treatment regimens and their modification during treatment. Meta-analyses of these studies suffer from the same sources of bias and only some of the biases can be accounted for by careful analysis of the methods.

We presented here only data on mortality. The original studies examined further outcomes including clinical cure and microbiological cure. We believe that for patients with severe infections caused by MDR Gram-negative bacteria survival is ultimately the only outcome that matters to the individual patient, while resistance development is relevant epidemiologically.

Systematically reviewing the evidence highlights areas of missing data. We are mostly missing RCTs examining treatment options for CRGNBs: the two polymyxins, different doses of the polymyxins, polymyxins vs. alternative antibiotics covering CRGNBs (e.g. aminoglycosides, tigecycline) and polymyxin monotherapy vs. specific combination therapies. These RCTs should examine mortality and resistance development, although the latter should also be examined in longitudinal studies befitting the timeframe of resistance development.

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