bioRxiv preprint doi: https://doi.org/10.1101/465559; this version posted November 8, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

Intravenous colistin use for infections due to multidrug-resistant gram-negative bacilli in critically ill paediatric patients: a systematic review and meta-analysis

Spyridon A. Karageorgos, MD,[1,2] Hamid Bassiri, MD, PhD,[2] George Siakallis, MD, MSc,[1] Michael Miligkos, MD, MSc, PhD,[1,3] Constantinos Tsioutis, MD, PhD [1,4*]

[1] Infectious Diseases Working Group, Society of Junior Doctors, Athens, Greece

[2] Division of Infectious Diseases and Center for Childhood Cancer Research, Children's Hospital of Philadelphia, Perelman School of Medicine at the University of Pennsylvania, USA.

[3] Laboratory of Biomathematics, University of Thessaly School of Medicine, Larissa, Greece

[4] School of Medicine, European University Cyprus, Nicosia, Cyprus

***Corresponding author:**

Constantinos Tsioutis, MD, PhD, School of Medicine, European University Cyprus, 6 Diogenis Str., Engomi, 1516 Nicosia, Cyprus, Tel: +35722559413, Fax: +35722559515, Email address: kostsioutis@gmail.com, k.tsioutis@euc.ac.cy

Abbreviated and Running title: Colistin in critically ill children

Keywords: colistin; multidrug resistance; paediatric; intensive care unit; systematic review.

bioRxiv preprint doi: https://doi.org/10.1101/465559; this version posted November 8, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

Synopsis

Background: Data are limited regarding the clinical effectiveness and safety of intravenous colistin for treatment of infections by multidrug-resistant gram-negative bacilli (MDR-GNB) in the paediatric intensive care unit (PICU).

Methods: Systematic review of intravenous colistin use in critically ill paediatric patients with MDR-GNB infection in PubMed, Scopus and Embase (through January 31st, 2018).

Results: Out of 1,181 citations, 7 studies were included on the use of intravenous colistin for 405 patients in PICU. Majority of patients were diagnosed with lower respiratory tract infections, with *Acinetobacter baumannii* being the predominant pathogen. Colistin dosages ranged between 2.6-18 mg/kg/day, with none but one case reporting a loading dose. Emergence of colistin-resistance during treatment was reported in two cases. Nephrotoxicity and neurotoxicity were reported in 6.1% and 0.5% respectively, but concomitant medications and severe underlying illness limited our ability to definitively associate use of colistin with nephrotoxicity. Crude mortality was 29.5% (95%CI 21.7-38.1%), whereas infection-related mortality was 16.6% (95%CI 12.2-21.5%).

Conclusions: While the reported incidence of adverse events related to colistin were low, reported mortality rates for infections by MDR-GNB in PICU were notable. In addition to severity of disease and comorbidities, inadequate daily dosage and the absence of a loading dose may have contributed to mortality. As the use of colistin for treatment of MDR-GNB infections increases, it is imperative to understand whether optimal dosing of colistin in paediatric patients differs across different age groups. As such, future studies to establish the pharmacokinetic properties of colistin in different paediatric settings are warranted.

bioRxiv preprint doi: https://doi.org/10.1101/465559; this version posted November 8, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

Introduction

The increased incidence of infections due to multidrug-resistant (MDR) or extensively-drug resistant (XDR) gram-negative bacilli (GNB), has a significant impact on patient safety and public health [1,2]. Given the paucity of effective antibiotics that are either available or in clinical development, clinicians have resorted to the use of older agents and combinational therapies for treatment of these infections [3].

Although epidemiological data in paediatric settings are limited, studies worldwide show that the antibiotic resistances of GNB are increasing at an alarming rate. For example, a recent report from the Antibiotic Resistance and Prescribing in European Children (ARPEC) project, demonstrated high rates of resistance to commonly used antibiotic classes in children, especially for *Escherichia coli*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* [4], while a national surveillance study among children between 1-17 years of age, revealed a two-fold increase of carbapenem-resistant *P. aeruginosa* in children in the USA from 1999 to 2012 [5]. In another study in European paediatric and neonatal intensive care units (ICU), resistance rates among GNB in intra-abdominal infections were higher than those recorded in non-ICU wards, with MDR rates reaching as high as 13.5% for *P. aeruginosa* and 40.5% for *K. pneumoniae* isolates, whereas the highest MDR rates were noted in Central (24.5% of isolates) and Southeast (11.5% of isolates) Europe [6]. Combinations of antibiotics are often necessary to treat these infections, and in endemic areas these combinations may even be used empirically, prior to confirmation of antibiotic susceptibilities. The limited clinical experience with the use of such treatment strategies in children and the lack of clinical trials involving use of new antibiotics in paediatric populations [7] further aggravate the situation.

bioRxiv preprint doi: https://doi.org/10.1101/465559; this version posted November 8, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

Colistin, which was discovered in 1949 and used since the 1950s has found a recent resurgence in use for treatment of infections by MDR- and XDR-GNB [8]. Although the dosing and safety profile of colistin have been extensively studied in adults, several issues remain unresolved in paediatric patients, particularly the pharmacokinetics and optimal dosing of children of different ages [8].

The aim of this systematic review was to evaluate the available evidence concerning the clinical effectiveness and safety of colistin in the treatment of infections due to MDR-GNB in the PICU.

Material and methods

Data Sources and Search

This review adopted the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [9]. We performed a literature search in PubMed, Scopus and Embase databases from 2000 through 2018 (last day of search was January 31st, 2018). The search term algorithm applied in PubMed was: (colistin OR polymyxin E) AND (child* OR pediatric* OR paediatric* OR toddler* OR adolescent*); whereas in Scopus and EMBASE the algorithm was: (colistin OR polymyxin B) AND (child OR children). The references of articles found in this manner were subsequently also searched for relevant articles that could meet the PRISMA criteria.

Study selection

Articles were eligible for inclusion, provided they fulfilled the following criteria: inclusion of at least 5 paediatric (defined as ≥1 month and ≤18 years of age) patients, and the use of intravenous colistin for treatment of infections due to MDR, XDR or

bioRxiv preprint doi: https://doi.org/10.1101/465559; this version posted November 8, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

pandrug-resistant GNB in a PICU setting. According to published definitions, a multidrug-resistant (MDR) pathogen is one that is resistant to at least 3 antibiotic classes, an extensively-drug-resistant (XDR) pathogen is resistant to all except one or two antibiotic classes, and a pandrug-resistant (PDR) pathogen is resistant to all antibiotic classes [1]. The following studies were excluded from analysis: studies conducted exclusively in patients with cystic fibrosis; studies that did not include colistin treatment outcomes; studies that included only neonates or were performed in a neonatal ICU; studies performed outside of the PICU; studies that used colistin for treatment of diarrhoea, for decontamination, or for prophylaxis; studies that used polymyxin B or polymyxin E formulations; studies exclusively concerning topical, oral, intraventricular, or intrathecal administration of colistin; conference abstracts, letters to the editor, articles without new data and reviews, and studies published in languages other than English. Authors of included studies were contacted for further clarifications when needed.

Outcomes and definitions

The primary outcome measure was all-cause mortality in patients who received intravenous colistin for treatment of the MDR- or XDR- or PDR- GNB infection. If available, infection-related mortality was also recorded. All reported outcome measures were classified according to the definitions provided by each study. The secondary outcomes of interest included the following: clinical cure/improvement; microbiological eradication of the original pathogen in a subsequent culture; number and type of adverse events which were either directly related or possibly related to colistin use, per the determination of the authors; and development of resistance to colistin during treatment. Nephrotoxicity and neurotoxicity were based on definitions

bioRxiv preprint doi: https://doi.org/10.1101/465559; this version posted November 8, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

used by each included study. The quality of the evidence regarding outcomes was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) algorithm [10].

Data extraction

Two investigators (CT and SAK) independently reviewed the titles and abstracts of the citations for potentially relevant articles using Abstrackr [11]; the full text publications of potentially relevant articles were retrieved and rescreened by the same two investigators. Disagreements were resolved by consensus with a third author (MM). Data were extracted by SAK and GS, using Excel® and included author, year, type of study, geographic region where study was conducted, number and characteristics of patients, their underlying diseases, severity of disease, type of infection, causative agents, site of pathogen isolation, colistin dosage, use of other forms of colistin (intraventricular/intrathecal, inhalation/nebulised, oral, topical), concomitant antibiotics, and outcomes as defined above.

Statistical analysis

We calculated the summary mortality rate and corresponding 95% confidence interval (CI), using the random-effects model with arcsine transformation for proportions [12]. We assessed statistical heterogeneity using the I2 statistic [13]. Statistical analysis was performed with OpenMetaAnalyst (http://www.cebm.brown.edu/open_meta/).

Results

Literature search

For this systematic review (Fig.1), we screened 1,181 non-duplicate citations; we

bioRxiv preprint doi: https://doi.org/10.1101/465559; this version posted November 8, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

excluded 1,030 as irrelevant and 151 articles were retrieved for full-text review. Study selection process is presented graphically in Figure 1. Of these, 7 studies met our inclusion criteria [14–20]. In one study, authors kindly provided clarifications and additional data [15]. All studies were retrospective and published between 2009 and 2018. Five studies were conducted in Asia [16–20] and two were conducted in Europe [14,15]. The majority of included studies were single arm retrospective cohorts; as a result the overall quality of the evidence that contributed to our systematic review was rated as low to very low [10].

Study characteristics

Data were available for 405 patients who received IV colistin for treatment of infections due to MDR-GNB [14–20]. Sixty one percent (248/405) of patients were male. The age of patients ranged from 1 month to 18 years. Data on patient demographics, underlying disorders, type of infections that warranted the initiation of colistin therapy, isolated microorganisms, site of pathogen isolation, and treatment, are presented in Table 1.

Type of infections and isolated pathogens

The most common infections that warranted use of colistin were lower respiratory tract infections (primarily ventilator-associated pneumonia), followed by bloodstream infection, urinary tract infection, central nervous system infection (including external ventricular drainage-associated ventriculitis or meningitis), and wound infection; sites from which these GNB were isolated are presented in Table 1. The most commonly isolated pathogen was *Acinetobacter baumannii*, followed by *P. aeruginosa* and *K. pneumoniae*. Other reported microorganisms were *Enterobacter cloacae, E. coli* and

bioRxiv preprint doi: https://doi.org/10.1101/465559; this version posted November 8, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

177 *Stenotrophomonas maltophilia*. The exact number of polymicrobial infections could
178 not be estimated, as this was not clarified in several of the studies.
179
180 ***Colistin treatment***
181 Concerning colistin dosage, 4 studies reported colistin dose in milligrams, ranging
182 from 2.6 to >9 mg/kg/day [14,17–20], two studies [15,16] reported colistin dose in
183 international units (IU), ranging from 40,000 to 225,000 IU/kg/day (estimated at 3.2-
184 18 mg/kg/day according to Ortwine et al [21]). Three studies reported that colistin
185 was administered in 3 divided daily doses [14,16,20]. A loading dose was reported in
186 one patient [15], consisting of 225,000 IU/kg (estimated at 18 mg/kg [21]). Mean
187 duration of colistin treatment was 10.8 to 31.6 days (range 2-133 days). In the
188 majority of included studies, colistin was used in combination therapy, most
189 commonly with carbapenems, glycopeptides, and aminoglycosides [14–17,19,20].
190 Three studies reported co-administration of IV colistin with other formulations of
191 colistin (aerosolised, intraventricular) as presented in Table 1 [15,17,19].
192
193 ***Mortality***
194 Mortality was reported in all included studies (405 patients) [14–20]. The summary
195 all- cause mortality was 29.5% (95% CI 21.7-38.1%, I^2=64.7%; Figure 2). In 6 studies
196 that reported an association between mortality and infection [14–17,19,20], the
197 infection-related mortality was 16.6% (95% CI 12.2-21.5%, I^2=13.1%,; Figure 3).
198
199 ***Clinical outcomes, microbiological eradication, and adverse events***
200 All studies provided information on secondary outcomes (Table 2). The summary
201 clinical cure/improvement, as defined by the study authors in 6 studies [14–16,18–20]

bioRxiv preprint doi: https://doi.org/10.1101/465559; this version posted November 8, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

was 73.1% (95% CI 64.4-81.0%, I^2=58.2; Figure 4). In one study, clinical cure/improvement was reported in 70/87 (80.4%) episodes [17].

In 5 studies that included data on follow-up cultures, microbiological eradication was confirmed in 150/206 (72.8%) of patients [14,16,19,20] and in 68/87 (78.2%) of episodes [17]. Development of resistance to colistin during therapy was reported in 2 patients, after prolonged use of intravenous and intraventricular colistin in one patient, and intravenous and aerosolised colistin in the other [15].

Data regarding adverse events were reported in all seven studies (Table 3) [14–20]. Nephrotoxicity (defined either as creatinine elevation from baseline or decrease of creatinine clearance during colistin treatment) was detected in 25/405 (6.1%) of patients. Notably, all patients with renal injury were either receiving concomitant nephrotoxic agents (such as vancomycin, aminoglycosides, radio contrast, or amphotericin B), or had pre-renal impairment or multiorgan failure. Management of renal impairment was reported in 5 patients as follows: colistin dose was adjusted in three [15,16], colistin was discontinued in one [17], and colistin was continued with renal replacement therapy in another [17]. In four patients [15,16,19] renal function returned to normal after colistin was adjusted or stopped, while three patients died of multiorgan failure [16]; the outcome of renal function was not reported in the remaining patients. Neurotoxicity was detected in 2/405 (0.5%) of patients [17]. Neurotoxicity was described as generalised tonic-clonic seizures on the first day of colistin administration without recurrence thereafter. Finally, in one study [16], four cases of microscopic haematuria in the context of disseminated intravascular coagulation were also reported.

Discussion

bioRxiv preprint doi: https://doi.org/10.1101/465559; this version posted November 8, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

MDR-GNB have emerged as a significant cause of infection in paediatric settings, resulting in increased morbidity and mortality [2,3]. Colistin, to which many of these MDR-GNB retain sensitivity, has gained increased use over the last decade [8], a fact that is supported by the observation that all included studies were published after 2009. In this systematic review, we found that colistin use had a relatively low rate of adverse events and resulted in favourable clinical outcome in 73.1% of paediatric patients with MDR-GNB infections hospitalised in a PICU setting, although the pooled and infection-related mortality rates were 29.5% and 16.6% respectively. It is also worth noting that the majority of included studies were conducted in countries that are known to have a high prevalence of MDR-GNB, signifying the importance of prudent use of colistin, to preserve its efficacy against these pathogens.

Our results demonstrate that the majority of MDR-GNB infections in the PICU treated with colistin were lower respiratory tract infections (and especially ventilator-associated pneumonia). Furthermore, we show that *A. baumannii* was the predominant pathogen, and most treated patients possessed significant comorbidities. Nonetheless, colistin achieved clinical improvement/cure and microbiological eradication in ~70% of infections. The observed pooled mortality rate in our study reflects that of critically ill children with severe infections observed in other multicentre [22,23] and single-centre [24–26] studies. Yet a previous systematic review of colistin use in children reported a lower crude mortality rate (7.4%) [27]. There are however, critical differences between these two studies: in the other study, not all patients were critically ill, MDR pathogens were infrequent, a proportion of patients were receiving systemic colistin for prophylaxis rather than treatment, and the majority of included studies were case reports. In support of our contention that these features may dramatically alter the mortality rates, adults treated with colistin for

bioRxiv preprint doi: https://doi.org/10.1101/465559; this version posted November 8, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

252 infections by carbapenem-resistant GNB had rates of clinical cure/improvement and
253 mortality that were more comparable to what we report, with estimated pooled
254 mortality rates between 33.8% - 35.7% [28,29].

255 As far as adverse events are concerned, colistin demonstrated a relatively good
256 rate of tolerability. The most frequently reported adverse event was nephrotoxicity,
257 detected in a small proportion of paediatric patients (6.1%). However, a clear causal
258 association with colistin could not be ascertained, since most of these patients
259 received concomitant nephrotoxic agents or had underlying conditions that
260 compromised renal function. These are factors that have been previously associated
261 with colistin-related nephrotoxicity in adults [30]. Of note, the reversibility of kidney
262 injury after cessation or dose adjustment of colistin, supports the necessity for
263 continuous awareness and frequent monitoring of renal function. Neurotoxicity
264 complicated only 0.5% of paediatric patients, and other adverse events were reported
265 in a small proportion. We believe that the lower rates of acute kidney injury and
266 neurotoxicity [27] reported in the previous systematic review of colistin use in
267 children are again attributable to the differences in the study characteristics. However,
268 it is worthy to note that the adverse event profile of colistin use in adults is different;
269 in a recent meta-analysis regarding the use of colistin in MDR-GNB infections,
270 colistin-related nephrotoxicity was noted to be much higher (19.2%), while
271 neurotoxicity was not reported [28].

272 The notable difference in rates of nephrotoxicity highlights the observation
273 that during childhood, various physiologic alterations affect drug pharmacokinetics
274 (e.g. volume of distribution, protein binding and renal clearance) and thus,
275 conclusions derived from adult studies do not readily apply to paediatric populations
276 [31], thus highlighting the need for future studies regarding the pharmacodynamics of

bioRxiv preprint doi: https://doi.org/10.1101/465559; this version posted November 8, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

277 colistin therapy in paediatric patients. Indeed, the need for a loading dose and the
278 optimal dosing of colistin is likely to vary between different age groups according to
279 renal function and body weight, or body surface area [31]. In support of this notion,
280 adult cases of nephrotoxicity have been associated with excessive colistin dosage,
281 owed to calculation of doses based on ideal body weight rather than actual body
282 weight [32]. Finally, future paediatric studies should employ strict definitions
283 regarding colistin-related clinical outcomes and adverse events, in order to better
284 evaluate the side effect profile of colistin and these studies should report all potential
285 colistin-related side effects instead of focusing primarily on the historically reported
286 ones (nephrotoxicity and neurotoxicity).

287 In closing, we would like to acknowledge two limitations of our study. Firstly,
288 the studies reported herein were all cohort studies; while this diminishes the quality of
289 evidence, we also cannot exclude an outcome reporting bias favouring the reporting
290 of successful treatments. Secondly, in one study [17] infection episodes were reported
291 rather than infected patients, making interpretations from this study difficult to
292 correlate to the number of affected children. Despite its shortcomings, our study
293 argues that colistin may be relatively safe to use in children with severe MDR-GNB
294 infections in which therapeutic options are limited.

295

296 **Conclusions**

297 In an era of increasing antimicrobial resistance, the present systematic review
298 suggests that colistin for infections by MDR-GNB in paediatric patients in the PICU
299 results in favourable clinical outcomes and has an acceptable safety profile. Until a
300 more robust understanding of the pharmacokinetics and pharmacodynamics of colistin
301 in various paediatric populations has been completed, colistin dosing should be

bioRxiv preprint doi: https://doi.org/10.1101/465559; this version posted November 8, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

carefully estimated in order to achieve maximum efficacy with the lowest possibility of adverse events, as this drug remains one of the last resorts for treatment of infections by MDR-GNB.

Ethical approval: Not required.

Funding: none to declare.

Transparency declarations: none to declare.

Author Contributions

Spyridon A. Karageorgos (SAK): conceptualised and designed the study, participated in data acquisition, extraction and interpretation, prepared tables, wrote and drafted the initial manuscript and approved the final manuscript as submitted.

Hamid Bassiri (HB): participated in data interpretation, reviewed and revised the manuscript and approved the final manuscript as submitted.

George Siakallis (GS): participated in data extraction and interpretation, reviewed and revised the initial manuscript and approved the final manuscript as submitted.

Michael Miligkos (MM): participated in data analysis and interpretation, reviewed and revised the initial manuscript and approved the final manuscript as submitted.

Constantinos Tsioutis (CT): conceptualised and designed the study, interpreted the data, wrote and drafted the initial manuscript, reviewed and revised the manuscript and approved the final manuscript as submitted.

bioRxiv preprint doi: https://doi.org/10.1101/465559; this version posted November 8, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

References

[1] Magiorakos A-P, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect 2012;18:268–81. doi:10.1111/j.1469-0691.2011.03570.x.

[2] Tacconelli E, Cataldo MA, Dancer SJ, De Angelis G, Falcone M, Frank U, et al. ESCMID guidelines for the management of the infection control measures to reduce transmission of multidrug-resistant Gram-negative bacteria in hospitalized patients. Clin Microbiol Infect 2014;20:1–55. doi:10.1111/1469-0691.12427.

[3] Lutsar I, Telling K, Metsvaht T. Treatment option for sepsis in children in the era of antibiotic resistance. Expert Rev Anti Infect Ther 2014;12:1237–52. doi:10.1586/14787210.2014.956093.

[4] Bielicki JA, Lundin R, Sharland M, others. Antibiotic resistance prevalence in routine bloodstream isolates from children's hospitals varies substantially from adult surveillance data in Europe. Pediatr Infect Dis J 2015;34:734–741.

[5] Logan LK, Gandra S, Mandal S, Klein EY, Levinson J, Weinstein RA, et al. Multidrug- and Carbapenem-Resistant Pseudomonas aeruginosa in Children, United States, 1999–2012. J Pediatr Infect Dis Soc 2016:piw064. doi:10.1093/jpids/piw064.

[6] Lob SH, Badal RE, Hackel MA, Sahm DF. Epidemiology and Antimicrobial Susceptibility of Gram-Negative Pathogens Causing Intra-abdominal Infections in Pediatric Patients in Europe—SMART 2011–2014. J Pediatr Infect Dis Soc 2016:piv109. doi:10.1093/jpids/piv109.

[7] Garazzino S, Lutsar I, Bertaina C, Tovo P-A, Sharland M. New antibiotics for paediatric use: A review of a decade of regulatory trials submitted to the European Medicines Agency from 2000—Why aren't we doing better? Int J Antimicrob Agents 2013;42:99–118. doi:10.1016/j.ijantimicag.2013.05.001.

[8] Nation RL, Li J, Cars O, Couet W, Dudley MN, Kaye KS, et al. Framework for optimisation of the clinical use of colistin and polymyxin B: the Prato polymyxin consensus. Lancet Infect Dis 2015;15:225–234.

[9] Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 2009;151:264–269.

[10] Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336:924–6.

[11] Wallace BC, Small K, Brodley CE, Lau J, Trikalinos TA. Deploying an interactive machine learning system in an evidence-based practice center: abstrackr. Proc ACM Int Health Inform Symp IHI 2012:819--824. doi:10.1145/2110363.2110464.

[12] Trikalinos TA, Trow P, Schmid CH. Simulation-Based Comparison of Methods for Meta-Analysis of Proportions and Rates. Rockville (MD): Agency for Healthcare Research and Quality (US); 2013.

[13] Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60. doi:10.1136/bmj.327.7414.557.

[14] Falagas ME, Sideri G, Vouloumanou EK, Papadatos JH, Kafetzis DA. Intravenous Colistimethate (Colistin) Use in Critically Ill Children Without

bioRxiv preprint doi: https://doi.org/10.1101/465559; this version posted November 8, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

Cystic Fibrosis: Pediatr Infect Dis J 2009;28:123–7. doi:10.1097/INF.0b013e31818a5dbd.

[15] Iosifidis E, Antachopoulos C, Ioannidou M, Mitroudi M, Sdougka M, Drossou-Agakidou V, et al. Colistin administration to pediatric and neonatal patients. Eur J Pediatr 2010;169:867–74. doi:10.1007/s00431-009-1137-3.

[16] Kapoor K, Jajoo M, Dublish S, Dabas V, Gupta S, Manchanda V. Intravenous Colistin for Multidrug-Resistant Gram-Negative Infections in Critically Ill Pediatric Patients: Pediatr Crit Care Med 2013;14:e268–72. doi:10.1097/PCC.0b013e31828a740f.

[17] Paksu MS, Paksu S, Karadag A, Sensoy G, Asilioglu N, Yildizdas D, et al. Old agent, new experience: colistin use in the paediatric Intensive Care Unit—a multicentre study. Int J Antimicrob Agents 2012;40:140–4. doi:10.1016/j.ijantimicag.2012.04.010.

[18] Phan PH, Nguyen TV. Colistin therapy for severe hospital-acquired infections caused by multidrug-resistant gramnegatve bacteria in pediatric patients. Pediatr Crit Care Med 2014;15:156.

[19] Polat M, Kara SS, Tapısız A, Tezer H, Kalkan G, Dolgun A. Treatment of Ventilator-Associated Pneumonia Using Intravenous Colistin Alone or in Combination with Inhaled Colistin in Critically Ill Children. Pediatr Drugs 2015;17:323–30. doi:10.1007/s40272-015-0133-5.

[20] Sahbudak Bal Z, Kamit Can F, Yazici P, Berna Anil A, Duyu M, Yilmaz Ciftdogan D, et al. The evaluation of safety and efficacy of colistin use in pediatric intensive care unit: Results from two reference hospitals and review of literature. J Infect Chemother 2018. doi:10.1016/j.jiac.2017.12.017.

[21] Ortwine JK, Kaye KS, Li J, Pogue JM. Colistin: Understanding and Applying Recent Pharmacokinetic Advances. Pharmacother J Hum Pharmacol Drug Ther 2015;35:11–6. doi:10.1002/phar.1484.

[22] Shime N, Kawasaki T, Saito O, Akamine Y, Toda Y, Takeuchi M, et al. Incidence and risk factors for mortality in paediatric severe sepsis: results from the national paediatric intensive care registry in Japan. Intensive Care Med 2012;38:1191–7. doi:10.1007/s00134-012-2550-z.

[23] Rosenthal VD, Maki DG, Jamulitrat S, Medeiros EA, Todi SK, Gomez DY, et al. International Nosocomial Infection Control Consortium (INICC) report, data summary for 2003-2008, issued June 2009. Am J Infect Control 2010;38:95–104.e2. doi:10.1016/j.ajic.2009.12.004.

[24] Karbuz A, Özdemir H, Yaman A, Kocabaş BA, Ödek Ç, Güriz H, et al. The Use of Colistin in Critically Ill Children in a Pediatric Intensive Care Unit: Pediatr Infect Dis J 2014;33:e19–24. doi:10.1097/INF.0000000000000117.

[25] Gupta A, Kapil A, Lodha R, Kabra SK, Sood S, Dhawan B, et al. Burden of healthcare-associated infections in a paediatric intensive care unit of a developing country: a single centre experience using active surveillance. J Hosp Infect 2011;78:323–6. doi:10.1016/j.jhin.2011.04.015.

[26] El-Nawawy A, Ashraf GA, Antonios MAM, Meheissen MA, El-Alfy MMR. Incidence of Multidrug-Resistant Organism Among Children Admitted to Pediatric Intensive Care Unit in a Developing Country. Microb Drug Resist 2018. doi:10.1089/mdr.2017.0414.

[27] Falagas ME, Vouloumanou EK, Rafailidis PI. Systemic colistin use in children without cystic fibrosis: a systematic review of the literature. Int J Antimicrob Agents 2009;33:503.e1-503.e13. doi:10.1016/j.ijantimicag.2008.10.021.

bioRxiv preprint doi: https://doi.org/10.1101/465559; this version posted November 8, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

[28] Ni W, Cai X, Wei C, Di X, Cui J, Wang R, et al. Efficacy of polymyxins in the treatment of carbapenem-resistant Enterobacteriaceae infections: a systematic review and meta-analysis. Braz J Infect Dis 2015;19:170–80. doi:10.1016/j.bjid.2014.12.004.

[29] Tsioutis C, Kritsotakis EI, Karageorgos SA, Stratakou S, Psarologakis C, Kokkini S, et al. Clinical epidemiology, treatment and prognostic factors of extensively drug-resistant Acinetobacter baumannii ventilator-associated pneumonia in critically ill patients. Int J Antimicrob Agents 2016;48:492–7. doi:10.1016/j.ijantimicag.2016.07.007.

[30] Pogue JM, Lee J, Marchaim D, Yee V, Zhao JJ, Chopra T, et al. Incidence of and Risk Factors for Colistin-Associated Nephrotoxicity in a Large Academic Health System. Clin Infect Dis 2011;53:879–84. doi:10.1093/cid/cir611.

[31] Kearns GL, Abdel-Rahman SM, Alander SW, Blowey DL, Leeder JS, Kauffman RE. Developmental pharmacology—drug disposition, action, and therapy in infants and children. N Engl J Med 2003;349:1157–1167.

[32] DeRyke CA, Crawford AJ, Uddin N, Wallace MR. Colistin Dosing and Nephrotoxicity in a Large Community Teaching Hospital. Antimicrob Agents Chemother 2010;54:4503–5. doi:10.1128/AAC.01707-09.

bioRxiv preprint doi: https://doi.org/10.1101/465559; this version posted November 8, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

Figure 1. Study selection

Figure 2. All-cause mortality

Figure 3. Infection-related mortality

Figure 4. Clinical cure/improvement

Table 1. Study Characteristics

Study, Country, Year [Ref]	No. patients (pts), or courses (crs) [male]	Mean age[a] (range)	Underlying disorders (no. patients)	Type of infection as reported by authors (no. patients)	Causative organism (no. patients)[b,c]	Site of pathogen isolation	Type of colistin formulation (add'l mode of delivery)	Dose of colistin and duration of treatment[a]	Concomitant therapeutic regimens (n patients)
Falagas et al Greece 2009	6 pts [5]	11y (14m-13y)	GM1 gangliosidosis (1) Cerebral palsy (1) None (4)	LRTI (4) BSI (1) LRTI+BSI (1)	PA (3) AB (2) KP+AB (1)	Bronchial secretions (4) Blood (1) Blood & bronchial secretions (1)	Colistimethate sodium (ND)	5mg/kg/d ÷3 doses Mean 10.7d	Piperacillin/tazobactam (1) Gentamicin (1) Imipenem/silastatin (1) Liposomal amphotericin B (1) Metronidazole (1) Vancomycin (1)
Iosifidis et al Greece 2010	12 pts 18 crs [5]	5y (1.5m-14y)	RDS, psychomotor retardation (2) Trauma (2) Hydrocephalus, EVD (1) TB meningitis, EVD (1) Meningomyelocele, hydrocephalus, EVD	RTI(4) CNS infection (2) BSI+RTI (2) BSI (1) Trauma (1) Trauma+ RTI (1)	AB (6) PA (1) ECl (1) AB+SM (1) AB+KP (1) KP+PA +SM (1)	Bronchial secretions (4) Blood & bronchial secretions (2) CSF (2) CSF and	Colistimethate sodium (3 IVT; 2 inhaled)	Range 40,000-225,000 IU/Kg/d Range 7-133d (3/12 rec'd <	Aminoglycosides (16/18 crs) Carbapenems (12/18 crs) Teicoplanin (5/18 crs) Vancomycin (4/18 crs) Metronidazole (4/18 crs) Fluconazole (4/18 crs) Amphotericin B (4/18 crs)

bioRxiv preprint doi: https://doi.org/10.1101/465559; this version posted November 8, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

			(1) Spinal tumor (1) Brain tumor+ leukemia (1) RDS+ seizures (1) Wilson disease+ liver transplantation (1) Respiratory failure+ obesity (1)	CNS infection+ RTI (1)	AB+KP+ PA +ECl(1)	bronchial secretions (2) Trauma and bronchial secretions (1) Trauma (1)		21d)	TMP/SMX (3/18 crs) Piperacillin/tazobactam (2/18 crs) Voriconazole (1/18 crs) Tigecycline (1/18 crs) Cloxacillin (1/18 crs) Clarithromycin (1/18 crs) Gancyclovir (1/18 crs) Anti-TB (1/18 crs)
Kapoor et al India 2013	50 pts [30]	36m (1m-12y)	Septic shock (29) Ileal perforation (3) Esophageal stricture (1)	CAP (18) VAP (12)	AB (35) PA (9) KP (7) ECo (3) ECl (1)	Endotracheal lavage (25) Blood (22) Urine (3) Pleural fluid (1) 5 pts with pos. cultures from >1 site with same organism	Colistin NOS	50,000-75,000 IU/Kg/d÷ 3 doses Mean 14.3d (range 7-21).	Meropenem (35) Piperacillin/sulbactam (10) Vancomycin (6) Fluconazole (4) Amphotericin B (2)
Paksu et al Turkey 2012	79 pts 87 crs [43]	30m	Chronic neurological/neuromuscular disease (26) Congenital heart disease (10) Primary immunodeficiency (8) Metabolic disorders	VAP (49) VAP+BSI (18) BSI (9) Sepsis (8) CNS infection (1) Soft tissue	AB (52/87) PA (16/87) KP (1/87) AB+PA+ KP (7/87) NR	Tracheal aspirate fluid (63/87) Blood (28/87) Skin swabs, conjunctival swabs (5/87)	Colistin NOS (1 IVT)	Mean±SD 5.4±0.6 mg/Kg/d Mean 17.2±8.4d (2-62)	Glycopeptides (36) Antifungal agents (32) Carbapenems (28) Aminoglycosides (27) Fluoroquinolones (12) Linezolid (12) Cefoperazone/sulbactam (8)

bioRxiv preprint doi: https://doi.org/10.1101/465559; this version posted November 8, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

			(7) Malignancy (2) Others (9)	infection (1) Peritonitis (1)	(11/87)	Others (peritoneal, CSF) (2/87)			Piperacillin/tazobactam (6) Antiviral agents (5) Others (8)
Phan et al Vietnam 2014	104 [73]	4m	NR	VAP (45)	AB, KP, PA consisted 92% of organisms	NR	Colistimethate sodium (NR)	Mean 6.2±1.2 mg/Kg/d Median 17d (IQR 11-23)	NR
Polat et al Turkey 2015[d]	32 [15] 18 [7]	18m 13.5m	Metabolic disorders (16) Chronic neurological/neuromuscular diseases (15) Malignancy (9) Chronic liver disease, Congenital hearty disease and thromboembolic events (6) Primary immunodeficiency (4)	VAP 50/50	AB (37) PA (13)		Colistimethate sodium (0) Colistimethate sodium (18 aerosolized)	3.2mg/kg/d (2.6-5 mg/kg/d). 16 days (10-22) 3.4mg/kg/d (2.8-5 mg/kg/d). 14 days (5-21)	Glycopeptides (33/50) Carbapenems (30/50) Aminoglycosides (21/50) Cefoperazome/sulbactam (9/50) Piperacillin/tazobactam (8/50) Fluoroquinolones (5/50)
Sahbudak Bal et al Turkey 2017	104 [70]	55.9m	Chronic neurological/ neuromuscular disorder (27) Congenital heart disease (14)	VAP (60) CLABSI+ sepsis (22) CLABSI+ VAP (7/)	AB (57/104) PA (25/104) KP	Endotracheal lavage 59 Blood 26 Urine 10 CSF 3	Colistin NOS (13 intrathecal)	5 mg/kg/day in 3 doses 12.5±6.4	Aminoglycosides 76/104 Glycopeptides 33/104 Amphotericin B 30/104 Meropenem 7/104 Antiviral agents

bioRxiv preprint doi: https://doi.org/10.1101/465559; this version posted November 8, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

			Chronic lung disease (11) Cancer (10) BM/solid transplantation (10) Primary immune deficiency (6) Chronic liver disease (6) Others (3)	CLABSI+ UTI (4) VAP+ UTI (3) UTI (3) Shunt infection (3) SSI (2)	(12/104) AB+KP+ PA (3/104) ECo (2/104) ECl (1/104)	Peritoneal fluid 2		(2-30) (mean±SD (range)	(aciclovir, ganciclovir) 6/104 Ciprofloxacin 5 TMP-SMX 2/104

AB=*A .baumannii;* BSI= Blood stream infection; CAP= community acquired pneumonia; CLABSI=Central line-associated bloodstream infection; CNS= Central nervous system; CSF= Cerebrospinal fluid; ECl= *E. coli*; ECo=*E. cloacae*; EVD= External ventricular device; IU= International units; IVT=Intraventricular; KP= *K. pneumoniae;* LRTI=Lower respiratory tract infection; m=months; ND=No data; NOS=not otherwise specified; NR= Not reported; PA=*P. aeruginosa*; PICU=Pediatric Intensive Care Unit; RDS= acute respiratory distress syndrome; RTI= Respiratory tract infection; SD=standard deviation; SM=*S. maltophilia*; SSI= Surgical site infection; TB=tuberculosis; TMP-SMX- trimethoprim-sulfamethoxazole; UTI=Urinary tract infection; VAP=Ventilator-associated pneumonia; y=years.

[a] Data are provided as medians (range) unless otherwise specified.

[b] Some infections were polymicrobial.

[c] All presented data refer to MDR GNB unless otherwise specified.

[d] Two patients were not admitted to the PICU during colistin administration

bioRxiv preprint doi: https://doi.org/10.1101/465559; this version posted November 8, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

bioRxiv preprint doi: https://doi.org/10.1101/465559; this version posted November 8, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

Table 2. Outcomes

Study, Year [Ref]	**No. patients**	**Clinical Cure/improvement**	**Definition of clinical cure/improvement**	**Microbio-logical eradication**	**Definition of microbiological eradication**	**Deaths (related to infection that required colistin therapy)**
Falagas et al 2009	6	6	Improvement of symptoms and signs of the index infection and the laboratory values	6	Eradication of the pathogen isolated initially by culture	2
Iosifidis et al 2010	12 (18 courses)	16/18 courses 10/12 patients	No clinical or laboratory signs of infection	ND	ND	2 (2 related to index infection)
Kapoor et al 2013	50	36	Resolving presenting signs and symptoms	44/46 with available follow up cultures	Absence of the same organism from the same site on follow up cultures	14 (all had MODS)
Paksu et al 2012[a]	87 episodes (79 patients)	70 episodes	Complete recovery from clinical findings of index infection at end of colistin treatment	68 episodes	Eradication of the causative microorganism in the final culture	12 (10 related to index infection)
Phan et al 2014	104	61	ND	ND	ND	44 (ND)
Polat et al 2015[b]	50	38	Clinical cure or improvement	38	Bacterial eradication (no growth of the causative organism on follow-up cultures regardless of clinical outcome)	20 (9 related to index infection)
Sahbudak Bal et al 2017	104	79	Complete recovery from clinical findings of	62	Culture clearance at the end of therapy	31 (15 related to index infection)

bioRxiv preprint doi: https://doi.org/10.1101/465559; this version posted November 8, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

			index infection			

[a] Numbers provided in episodes.

MODS= Multiple organ dysfunction syndrome; ND= No data

bioRxiv preprint doi: https://doi.org/10.1101/465559; this version posted November 8, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

Table 3. Adverse events

Study, Year [Ref]	No. patients	Patients with nephrotoxicity	Definition of nephrotoxicity	Patients with neuro-toxicity	Definition of neurotoxicity	Patients with other adverse events
Falagas et al 2009	6	0	2-fold increase in creatinine from baseline to >1.3 mg/dL	0	Level of consciousness, seizures, visual disturbance, neuromuscular blockade	0
Iosifidis et al 2010	12 (18 courses)	1	Elevation of creatinine values beyond the estimated normal range for age	0	Neuromuscular blockade, seizures, disturbance of consciousness	0
Kapoor et al 2013	50	5* (3 with MODS, 2 with concomitant vancomycin) (nephrotoxicity at 3rd-6th day of treatment)	2-fold increase in creatinine from baseline or a 30% decrease in creatinine clearance	0	Level of consciousness, seizures, visual disturbance, neuromuscular blockade	4 (microscopic hematuria in the context of DIC)
Paksu et al 2012	79 (87 episodes)	2 (both with concomitant gentamicin) (1 developed at day 8)	Serum creatinine >1.1 mg/dL or a 50% reduction in creatinine clearance or need for renal replacement therapy at any time	2 (tonic-clonic seizures)	Neuromuscular blockade, seizures, change in level of consciousness	0
Phan et al 2014	104	5 (all with MODS)	ND	0	ND	0
Polat et al 2015	50	1* (concomitant vancomycin & radiocontrast) (day 8)	Increase in serum creatinine by ≥50 % from the baseline and/or elevation of serum creatinine beyond the estimated normal range for age	0	ND	ND
Sahbudak Bal et al	104	11 (all with concomitant	Blood creatinine level >1.2	0	Paresthesia, neuromuscular	0

bioRxiv preprint doi: https://doi.org/10.1101/465559; this version posted November 8, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

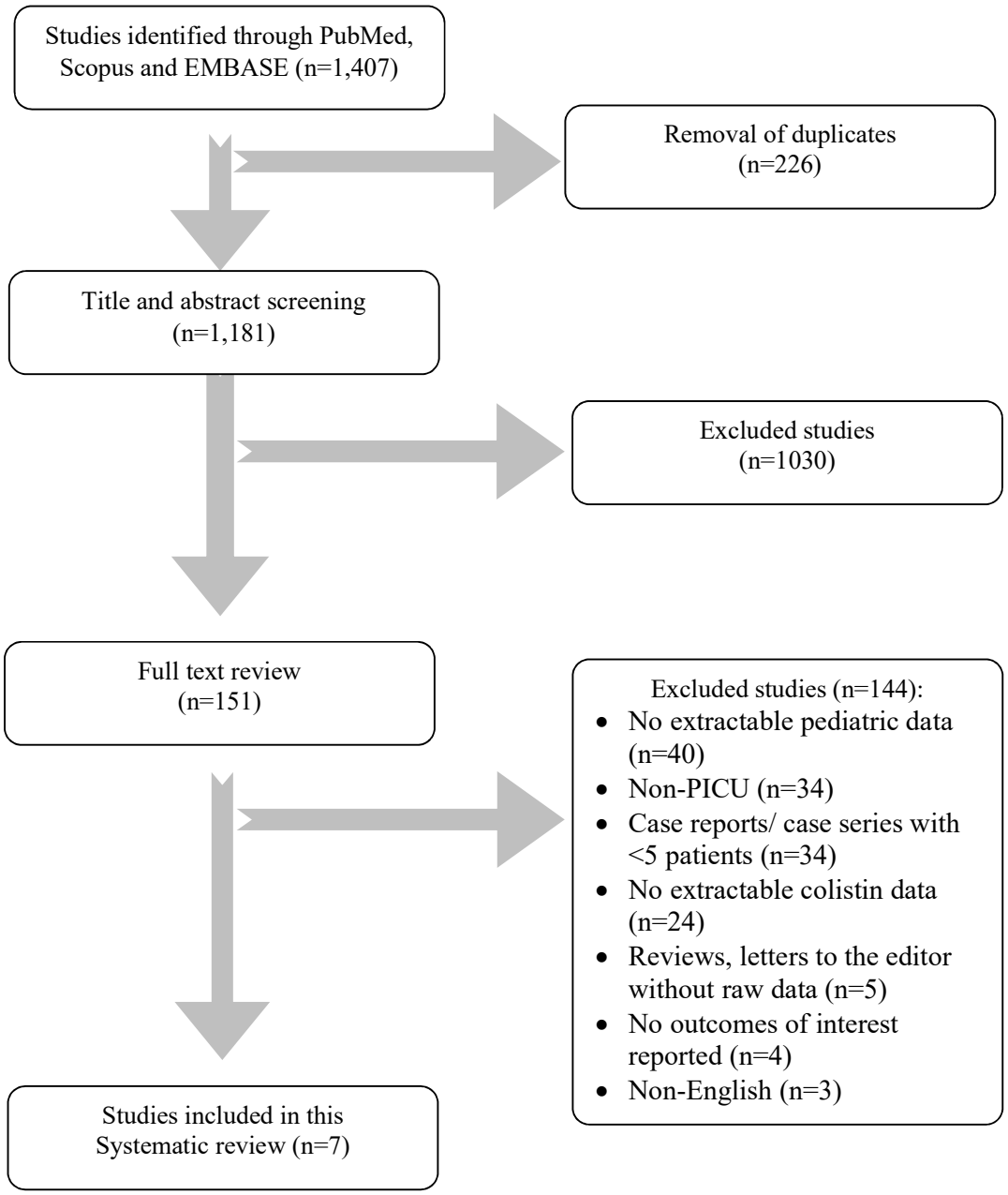
2017		nephrotoxic agents) (4 at day 0-3 6 at day 3-7 1 at day 7-14)	mg/dL or an increase of 50% above baseline creatinine or a decline in renal function		blockade, seizures, change in level of consciousness	

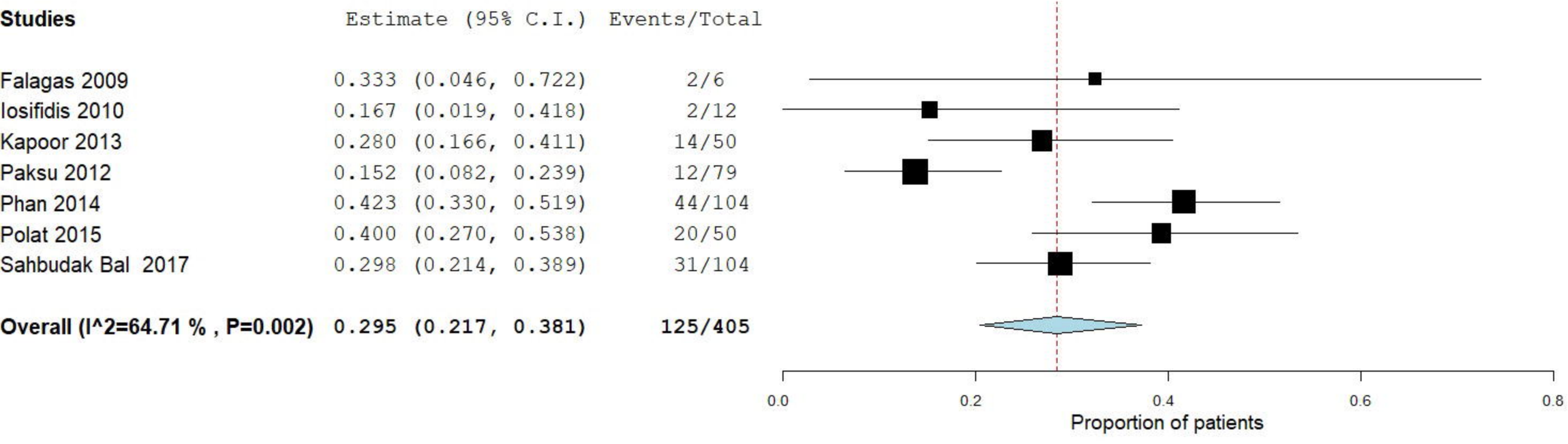
*: Not clearly related to colistin use.

DIC= Disseminated intravascular coagulation; MODS= Multiple organ dysfunction syndrome; ND= No data.

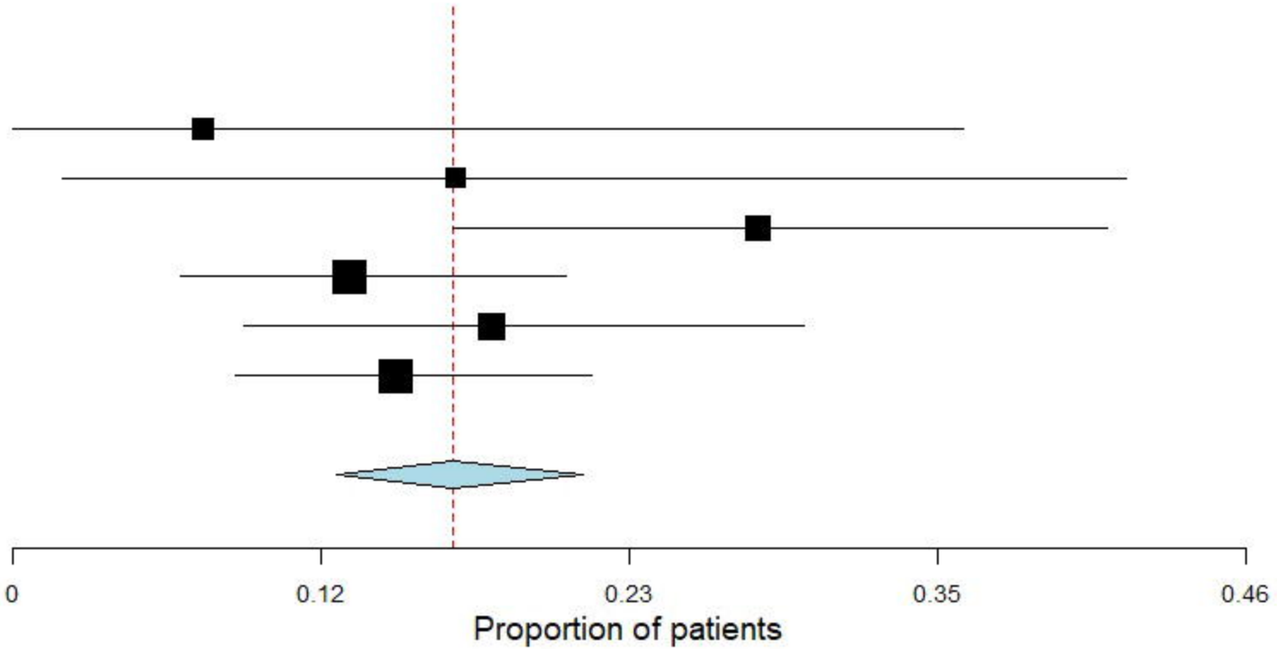
bioRxiv preprint doi: https://doi.org/10.1101/465559; this version posted November 8, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

Figure 1. Study selection




Studies
Estimate (95% C.I.)
Events/Total
Falagas 2009
0.333 (0.046, 0.722)
2/6
Iosifidis 2010
0.167 (0.019, 0.418)
2/12
Kapoor 2013
0.280 (0.166, 0.411)
14/50
Paksu 2012
0.152 (0.082, 0.239)
12/79
Phan 2014
0.423 (0.330, 0.519)
44/104
Polat 2015
0.400 (0.270, 0.538)
20/50
Sahbudak Bal 2017
0.298 (0.214, 0.389)
31/104
Overall (I^2=64.71 % , P=0.002)
0.295 (0.217, 0.381)
125/405
0.0
0.2
0.4
0.6
0.8
Proportion of patients

Studies	Estimate (95% C.I.)	Events/Total
Falagas 2009	0.071 (0.000, 0.358)	0/6
Iosifidis 2010	0.167 (0.019, 0.418)	2/12
Kapoor 2013	0.280 (0.166, 0.411)	14/50
Paksu 2012	0.127 (0.063, 0.208)	10/79
Polat 2015	0.180 (0.087, 0.297)	9/50
Sahbudak Bal 2017	0.144 (0.084, 0.218)	15/104
Overall (I^2=13.06 % , P=0.321)	**0.166 (0.122, 0.215)**	**50/301**



Studies	Estimate (95% C.I.)	Events/Total
Falagas 2009	0.929 (0.642, 1.000)	6/6
Iosifidis 2010	0.833 (0.582, 0.981)	10/12
Kapoor 2013	0.720 (0.589, 0.834)	36/50
Phan 2014	0.587 (0.491, 0.679)	61/104
Polat 2015	0.760 (0.633, 0.867)	38/50
Sahbudak Bal 2017	0.760 (0.673, 0.836)	79/104
Overall (I^2=58.24 % , P=0.028)	**0.731 (0.644, 0.810)**	**230/326**