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

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26 **Synopsis**

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

30 Methods: Systematic review of intravenous colistin use in critically ill paediatric
31 patients with MDR-GNB infection in PubMed, Scopus and Embase (through January
32 31st, 2018).

33 Results: Out of 1,181 citations, 7 studies were included on the use of intravenous
34 colistin for 405 patients in PICU. Majority of patients were diagnosed with lower
35 respiratory tract infections, with *Acinetobacter baumannii* being the predominant
36 pathogen. Colistin dosages ranged between 2.6-18 mg/kg/day, with none but one case
37 reporting a loading dose. Emergence of colistin-resistance during treatment was
38 reported in two cases. Nephrotoxicity and neurotoxicity were reported in 6.1% and
39 0.5% respectively, but concomitant medications and severe underlying illness limited
40 our ability to definitively associate use of colistin with nephrotoxicity. Crude
41 mortality was 29.5% (95%CI 21.7-38.1%), whereas infection-related mortality was
42 16.6% (95%CI 12.2-21.5%).

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

51

52 **Introduction**

53 The increased incidence of infections due to multidrug-resistant (MDR) or
 54 extensively-drug resistant (XDR) gram-negative bacilli (GNB), has a significant
 55 impact on patient safety and public health [1,2]. Given the paucity of effective
 56 antibiotics that are either available or in clinical development, clinicians have resorted
 57 to the use of older agents and combinational therapies for treatment of these infections
 58 [3].

59 Although epidemiological data in paediatric settings are limited, studies
 60 worldwide show that the antibiotic resistances of GNB are increasing at an alarming
 61 rate. For example, a recent report from the Antibiotic Resistance and Prescribing in
 62 European Children (ARPEC) project, demonstrated high rates of resistance to
 63 commonly used antibiotic classes in children, especially for *Escherichia coli*,
 64 *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* [4], while a national
 65 surveillance study among children between 1-17 years of age, revealed a two-fold
 66 increase of carbapenem-resistant *P. aeruginosa* in children in the USA from 1999 to
 67 2012 [5]. In another study in European paediatric and neonatal intensive care units
 68 (ICU), resistance rates among GNB in intra-abdominal infections were higher than
 69 those recorded in non-ICU wards, with MDR rates reaching as high as 13.5% for *P.*
 70 *aeruginosa* and 40.5% for *K. pneumoniae* isolates, whereas the highest MDR rates
 71 were noted in Central (24.5% of isolates) and Southeast (11.5% of isolates) Europe
 72 [6]. Combinations of antibiotics are often necessary to treat these infections, and in
 73 endemic areas these combinations may even be used empirically, prior to
 74 confirmation of antibiotic susceptibilities. The limited clinical experience with the use
 75 of such treatment strategies in children and the lack of clinical trials involving use of
 76 new antibiotics in paediatric populations [7] further aggravate the situation.

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

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

116

Outcomes and definitions

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

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

152 excluded 1,030 as irrelevant and 151 articles were retrieved for full-text review. Study
153 selection process is presented graphically in Figure 1. Of these, 7 studies met our
154 inclusion criteria [14–20]. In one study, authors kindly provided clarifications and
155 additional data [15]. All studies were retrospective and published between 2009 and
156 2018. Five studies were conducted in Asia [16–20] and two were conducted in Europe
157 [14,15]. The majority of included studies were single arm retrospective cohorts; as a
158 result the overall quality of the evidence that contributed to our systematic review was
159 rated as low to very low [10].

160

161 *Study characteristics*

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

168

169 *Type of infections and isolated pathogens*

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

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]

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

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

209 Data regarding adverse events were reported in all seven studies (Table 3)
210 [14–20]. Nephrotoxicity (defined either as creatinine elevation from baseline or
211 decrease of creatinine clearance during colistin treatment) was detected in 25/405
212 (6.1%) of patients. Notably, all patients with renal injury were either receiving
213 concomitant nephrotoxic agents (such as vancomycin, aminoglycosides, radio
214 contrast, or amphotericin B), or had pre-renal impairment or multiorgan failure.
215 Management of renal impairment was reported in 5 patients as follows: colistin dose
216 was adjusted in three [15,16], colistin was discontinued in one [17], and colistin was
217 continued with renal replacement therapy in another [17]. In four patients [15,16,19]
218 renal function returned to normal after colistin was adjusted or stopped, while three
219 patients died of multiorgan failure [16]; the outcome of renal function was not
220 reported in the remaining patients. Neurotoxicity was detected in 2/405 (0.5%) of
221 patients [17]. Neurotoxicity was described as generalised tonic-clonic seizures on the
222 first day of colistin administration without recurrence thereafter. Finally, in one study
223 [16], four cases of microscopic haematuria in the context of disseminated
224 intravascular coagulation were also reported.

225

226 **Discussion**

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

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

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

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

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

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

Conclusions

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

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.

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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.

324 **References**

- 325 [1] Magiorakos A-P, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, et
326 al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria:
327 an international expert proposal for interim standard definitions for acquired
328 resistance. *Clin Microbiol Infect* 2012;18:268–81. doi:10.1111/j.1469-
329 0691.2011.03570.x.
- 330 [2] Tacconelli E, Cataldo MA, Dancer SJ, De Angelis G, Falcone M, Frank U, et al.
331 ESCMID guidelines for the management of the infection control measures to
332 reduce transmission of multidrug-resistant Gram-negative bacteria in
333 hospitalized patients. *Clin Microbiol Infect* 2014;20:1–55. doi:10.1111/1469-
334 0691.12427.
- 335 [3] Lutsar I, Telling K, Metsvaht T. Treatment option for sepsis in children in the
336 era of antibiotic resistance. *Expert Rev Anti Infect Ther* 2014;12:1237–52.
337 doi:10.1586/14787210.2014.956093.
- 338 [4] Bielicki JA, Lundin R, Sharland M, others. Antibiotic resistance prevalence in
339 routine bloodstream isolates from children’s hospitals varies substantially from
340 adult surveillance data in Europe. *Pediatr Infect Dis J* 2015;34:734–741.
- 341 [5] Logan LK, Gandra S, Mandal S, Klein EY, Levinson J, Weinstein RA, et al.
342 Multidrug- and Carbapenem-Resistant *Pseudomonas aeruginosa* in Children,
343 United States, 1999–2012. *J Pediatr Infect Dis Soc* 2016:piw064.
344 doi:10.1093/jpids/piw064.
- 345 [6] Lob SH, Badal RE, Hackel MA, Sahm DF. Epidemiology and Antimicrobial
346 Susceptibility of Gram-Negative Pathogens Causing Intra-abdominal Infections
347 in Pediatric Patients in Europe—SMART 2011–2014. *J Pediatr Infect Dis Soc*
348 2016:piv109. doi:10.1093/jpids/piv109.
- 349 [7] Garazzino S, Lutsar I, Bertaina C, Tovo P-A, Sharland M. New antibiotics for
350 paediatric use: A review of a decade of regulatory trials submitted to the
351 European Medicines Agency from 2000—Why aren’t we doing better? *Int J*
352 *Antimicrob Agents* 2013;42:99–118. doi:10.1016/j.ijantimicag.2013.05.001.
- 353 [8] Nation RL, Li J, Cars O, Couet W, Dudley MN, Kaye KS, et al. Framework for
354 optimisation of the clinical use of colistin and polymyxin B: the Prato polymyxin
355 consensus. *Lancet Infect Dis* 2015;15:225–234.
- 356 [9] Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for
357 systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med*
358 2009;151:264–269.
- 359 [10] Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et
360 al. GRADE: an emerging consensus on rating quality of evidence and strength of
361 recommendations. *BMJ* 2008;336:924–6.
- 362 [11] Wallace BC, Small K, Brodley CE, Lau J, Trikalinos TA. Deploying an
363 interactive machine learning system in an evidence-based practice center:
364 abstrackr. *Proc ACM Int Health Inform Symp IHI* 2012:819–824.
365 doi:10.1145/2110363.2110464.
- 366 [12] Trikalinos TA, Trow P, Schmid CH. Simulation-Based Comparison of Methods
367 for Meta-Analysis of Proportions and Rates. Rockville (MD): Agency for
368 Healthcare Research and Quality (US); 2013.
- 369 [13] Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in
370 meta-analyses. *BMJ* 2003;327:557–60. doi:10.1136/bmj.327.7414.557.
- 371 [14] Falagas ME, Sideri G, Vouloumanou EK, Papadatos JH, Kafetzis DA.
372 Intravenous Colistimethate (Colistin) Use in Critically Ill Children Without

- 373 Cystic Fibrosis: *Pediatr Infect Dis J* 2009;28:123–7.
374 doi:10.1097/INF.0b013e31818a5dbd.
- 375 [15] Iosifidis E, Antachopoulos C, Ioannidou M, Mitroudi M, Sdougka M, Drossou-
376 Agakidou V, et al. Colistin administration to pediatric and neonatal patients. *Eur*
377 *J Pediatr* 2010;169:867–74. doi:10.1007/s00431-009-1137-3.
- 378 [16] Kapoor K, Jajoo M, Dublish S, Dabas V, Gupta S, Manchanda V. Intravenous
379 Colistin for Multidrug-Resistant Gram-Negative Infections in Critically Ill
380 Pediatric Patients: *Pediatr Crit Care Med* 2013;14:e268–72.
381 doi:10.1097/PCC.0b013e31828a740f.
- 382 [17] Paksu MS, Paksu S, Karadag A, Sensoy G, Asilioglu N, Yildizdas D, et al. Old
383 agent, new experience: colistin use in the paediatric Intensive Care Unit—a
384 multicentre study. *Int J Antimicrob Agents* 2012;40:140–4.
385 doi:10.1016/j.ijantimicag.2012.04.010.
- 386 [18] Phan PH, Nguyen TV. Colistin therapy for severe hospital-acquired infections
387 caused by multidrug-resistant gramnegative bacteria in pediatric patients. *Pediatr*
388 *Crit Care Med* 2014;15:156.
- 389 [19] Polat M, Kara SS, Tapisiz A, Tezer H, Kalkan G, Dolgun A. Treatment of
390 Ventilator-Associated Pneumonia Using Intravenous Colistin Alone or in
391 Combination with Inhaled Colistin in Critically Ill Children. *Pediatr Drugs*
392 2015;17:323–30. doi:10.1007/s40272-015-0133-5.
- 393 [20] Sahbudak Bal Z, Kamit Can F, Yazici P, Berna Anil A, Duyu M, Yilmaz
394 Ciftoglu D, et al. The evaluation of safety and efficacy of colistin use in
395 pediatric intensive care unit: Results from two reference hospitals and review of
396 literature. *J Infect Chemother* 2018. doi:10.1016/j.jiac.2017.12.017.
- 397 [21] Ortwin JK, Kaye KS, Li J, Pogue JM. Colistin: Understanding and Applying
398 Recent Pharmacokinetic Advances. *Pharmacother J Hum Pharmacol Drug Ther*
399 2015;35:11–6. doi:10.1002/phar.1484.
- 400 [22] Shime N, Kawasaki T, Saito O, Akamine Y, Toda Y, Takeuchi M, et al.
401 Incidence and risk factors for mortality in paediatric severe sepsis: results from
402 the national paediatric intensive care registry in Japan. *Intensive Care Med*
403 2012;38:1191–7. doi:10.1007/s00134-012-2550-z.
- 404 [23] Rosenthal VD, Maki DG, Jamulitrat S, Medeiros EA, Todi SK, Gomez DY, et
405 al. International Nosocomial Infection Control Consortium (INICC) report, data
406 summary for 2003-2008, issued June 2009. *Am J Infect Control* 2010;38:95–
407 104.e2. doi:10.1016/j.ajic.2009.12.004.
- 408 [24] Karbuz A, Özdemir H, Yaman A, Kocabaş BA, Ödek Ç, Güriz H, et al. The Use
409 of Colistin in Critically Ill Children in a Pediatric Intensive Care Unit: *Pediatr*
410 *Infect Dis J* 2014;33:e19–24. doi:10.1097/INF.0000000000000117.
- 411 [25] Gupta A, Kapil A, Lodha R, Kabra SK, Sood S, Dhawan B, et al. Burden of
412 healthcare-associated infections in a paediatric intensive care unit of a
413 developing country: a single centre experience using active surveillance. *J Hosp*
414 *Infect* 2011;78:323–6. doi:10.1016/j.jhin.2011.04.015.
- 415 [26] El-Nawawy A, Ashraf GA, Antonios MAM, Meheissen MA, El-Alfy MMR.
416 Incidence of Multidrug-Resistant Organism Among Children Admitted to
417 Pediatric Intensive Care Unit in a Developing Country. *Microb Drug Resist*
418 2018. doi:10.1089/mdr.2017.0414.
- 419 [27] Falagas ME, Vouloumanou EK, Rafailidis PI. Systemic colistin use in children
420 without cystic fibrosis: a systematic review of the literature. *Int J Antimicrob*
421 *Agents* 2009;33:503.e1-503.e13. doi:10.1016/j.ijantimicag.2008.10.021.

- 422 [28] Ni W, Cai X, Wei C, Di X, Cui J, Wang R, et al. Efficacy of polymyxins in the
423 treatment of carbapenem-resistant Enterobacteriaceae infections: a systematic
424 review and meta-analysis. *Braz J Infect Dis* 2015;19:170–80.
425 doi:10.1016/j.bjid.2014.12.004.
- 426 [29] Tsioutis C, Kritsotakis EI, Karageorgos SA, Stratakou S, Psarologakis C,
427 Kokkini S, et al. Clinical epidemiology, treatment and prognostic factors of
428 extensively drug-resistant *Acinetobacter baumannii* ventilator-associated
429 pneumonia in critically ill patients. *Int J Antimicrob Agents* 2016;48:492–7.
430 doi:10.1016/j.ijantimicag.2016.07.007.
- 431 [30] Pogue JM, Lee J, Marchaim D, Yee V, Zhao JJ, Chopra T, et al. Incidence of
432 and Risk Factors for Colistin-Associated Nephrotoxicity in a Large Academic
433 Health System. *Clin Infect Dis* 2011;53:879–84. doi:10.1093/cid/cir611.
- 434 [31] Kearns GL, Abdel-Rahman SM, Alander SW, Blowey DL, Leeder JS, Kauffman
435 RE. Developmental pharmacology—drug disposition, action, and therapy in
436 infants and children. *N Engl J Med* 2003;349:1157–1167.
- 437 [32] DeRyke CA, Crawford AJ, Uddin N, Wallace MR. Colistin Dosing and
438 Nephrotoxicity in a Large Community Teaching Hospital. *Antimicrob Agents*
439 *Chemother* 2010;54:4503–5. doi:10.1128/AAC.01707-09.
440

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) ECI (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)

			(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 +ECI(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) ECI (1)	Endotrachea l 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/neuromu sclar 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)

			(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 heart 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) Cefoperazone/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

			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) ECI (1/104)	Peritoneal fluid 2		(2-30) (mean±SD (range)	(aciclovir, ganciclovir) 6/104 Ciprofloxacin 5 TMP-SMX 2/104
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AB=*A. baumannii*; BSI= Blood stream infection; CAP= community acquired pneumonia; CLABSI=Central line-associated bloodstream infection; CNS= Central nervous system; CSF= Cerebrospinal fluid; ECI= *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

Table 2. Outcomes

Study, Year [Ref]	No. patients	Clinical Cure/improvement	Definition of clinical cure/improvement	Microbiological 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)

			index infection			
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^a Numbers provided in episodes.

MODS= Multiple organ dysfunction syndrome; ND= No data

Table 3. Adverse events

Study, Year [Ref]	No. patients	Patients with nephrotoxicity	Definition of nephrotoxicity	Patients with neurotoxicity	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 3 rd -6 th 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

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	
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*: Not clearly related to colistin use.

DIC= Disseminated intravascular coagulation; MODS= Multiple organ dysfunction syndrome;

ND= No data.

Figure 1. Study selection

Studies	Estimate (95% C.I.)	Events/Total
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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
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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 (I²=58.24 % , P=0.028)	0.731 (0.644, 0.810)	230/326