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REVIEW

Combination antibiotic treatment versus monotherapy for multidrug-resistant, extensively drug-resistant, and pandrug-resistant *Acinetobacter* infections: a systematic review

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Abstract Controversy surrounds combination treatment or monotherapy against multidrug-resistant (MDR), extensively drug-resistant (XDR), and pandrug-resistant (PDR) *Acinetobacter* infections in clinical practice. We searched the PubMed and Scopus databases for studies reporting on the clinical outcomes of patients infected with MDR, XDR, and PDR *Acinetobacter* spp. with regard to the administered intravenous antibiotic treatment. Twelve studies reporting on 1,040 patients suffering from 1,044 infectious episodes of MDR *Acinetobacter* spp. were included. The overall mortality between studies varied from 28.6 to 70 %; from 25 to 100 % in the monotherapy arm and from 27 to 57.1 % in the combination arm. Combination treatment was superior to monotherapy in three studies, where carbapenem with ampicillin/sulbactam (mortality 30.8 %, $p=0.012$), carbapenem with colistin (mortality 23 %, $p=0.009$), and combinations of colistin with rifampicin, sulbactam with aminoglycosides, tigecycline with colistin and rifampicin, and tigecycline with rifampicin and amikacin (mortality 27 %, $p<0.05$) were used against MDR *Acinetobacter* spp. resistant at least to carbapenems. The benefit was not validated in the remaining studies. Clinical success varied from 42.4 to 76.9 % and microbiological eradication varied from 32.7 to 67.3 %. Adverse events referred mainly to polymixins nephrotoxicity that varied from 19 to 50 %. The emergence of resistance was noted with tigecycline regimens in off-label uses in three studies. The available data preclude a firm recommendation with regard to combination treatment or monotherapy. For the time being, combination treatment may be preferred for severely ill patients. We urge for randomized controlled trials examining the optimal treatment of infections due to MDR, XDR, and PDR *Acinetobacter* spp.

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Introduction

In the 1960s, *Acinetobacter* spp. was considered to be a commensal pathogen with limited clinical significance. However, the incidence of *Acinetobacter* spp. infections have increased in the past several decades, especially in intensive care unit (ICU) patients [1, 2], and this may be attributed to the medical progress with concern to critically ill patients that resulted in an increase of the vulnerable population.

Acinetobacter spp. have also attracted attention because they easily adopt resistance mechanisms, such as the production of β-lactamases and efflux pumps, lower permeability of the outer membrane, mutations in antibiotic targets, and production of aminoglycoside-inactivating enzymes [3]. Noteworthy, multidrug-resistant (MDR), extensively drug-resistant (XDR), as well as pandrug-resistant (PDR) strains have emerged [4, 5], with grave clinical implications.

Treatment options for *Acinetobacter* spp. infections include sulbactam, antipseudomonal penicillins, antipseudomonal cephalosporins, antipseudomonal carbapenems, monobactams, aminoglycosides, fluoroquinolones, tetracyclines, glycylcyclines, and polymyxins [3]. Controversy surrounds treatment issues with regard to the effectiveness and emergence of resistant strains in clinical practice. Combination therapy or monotherapy and optimal treatment regimens for MDR *Acinetobacter* spp. infections are not yet defined [6].

Table 1 Characteristics and outcomes of the studies reporting on the treatment of multidrug-resistant (MDR), extensively drug-resistant (XDR), or pandrug-resistant (PDR) *Acinetobacter* infections

First author, year	Study period	Study design	Number of pts; site of infection	Patient characteristics; co-morbidity	*Acinetobacter* susceptibility pattern	Antibiotic treatment (*n*); mortality (%)		Statistical analyses on mortality	Clinical success (%) (combo vs. mono)	Eradication (%) (combo vs. mono)	Adverse events (%) (combo vs. mono)	Emergence of resistance (combo. vs. mono.)	Comments
						Combination	Monotherapy						
Betrosian, 2008 [24]	NR	Prospective	28; VAP	Mean age (years): 67±9 (mono), 72±5 (combo), mean APACHE II score: 14	XDR (COS)	NA	28-day coli: 15; 33.3 ;% asm[a]: 13; 23.1 ;%	No sig. difference in mortality (14-day or 28-day) between the compared groups	60 ;% coli, 61.5 ;% asm, *p*=NS	Eradication, 46.6 ;% coli vs. 46.1 ;% asm. Bacteriological success, 66.6 ;% (10/15) coli vs. 61.5 ;% (8/13) asm, *p*=NS	Nephrotoxicity: 33.3 ;% coli vs. 15 ;% asm. Temporary skin rash and diarrhea in 2 pts in the asm group	NR	No
Durante-Mangoni, 2013 [21]	2008–2011	RCT	209; 144 VAP, 18 HAP, 42 BSI, 5 complicated IAI	ICU patients, mean age (years): 62 ±15.4, SAPS II score: 39.9±11	XDR (COS)	Coli+rif: 104; 43.3 ;% (30-day), 21.2 ;% infection-related	Coli: 105; 42.9 ;% (30-day), 26.7 ;% (infection-related)	No sig. difference in 30-day or in infection-related mortality	NR	60.6 ;% coli+rif, 44.8 ;% coli, *p*=0.03	Renal dysfunction (23.7 ;% vs. 28.7 ;%, *p*=NS), hepatic dysfunction (20.8 % vs. 11.9 ;%, *p*=NS), neurotoxicity (0.99 ;% vs. 0 ;%, *p*=NS)	None	Colistin and rifampicin were significantly associated with eradication but not survival
Gounden, 2009 [25]	2003–2005	Retrospective	64; source of isolation: 20 blood, 50 respiratory secretions, 17 wound, 1 CSF, 1 CVC, 9 urine	ICU patients; mean age (years): 43.5 ±15.6 (coli), 45.6±18.2 (tobra), mean APACHE II score: 14.4±5.1 (coli), 14.8±5.4 (tobra)	Coli group: all XDR (COS); tobra group: 75 ;% CR	NA	Coli: 32; 34.4 ;% (ICU mortality), 50 ;% (in-hospital mortality); tobra: 32; 21.9 ;% (ICU mortality), 28.1 ;% (in-hospital mortality)	NR	NR	50 ;% (coli) vs. 55 ;% (tobra) *p*=NS	Increase in creatinine over 50 ;%: 19 ;% (coli) vs. 8.7 ;% (tobra), *p*=NS	NR	No sig. difference in ICU mortality, eradication, and nephrotoxicity between the arms. Higher in-hospital mortality for colistin than tobramycin (HR=0.43, 95 ;% CI: 0.19–0.99)
Hernández-Torres 2012, [17]	2007–2008	Prospective	77 (7 did not receive treatment); source of isolates: 27 blood, 47 respiratory tract, 8 urinary tract, 24 CVC, 1 CNS	83 ;% ICU patients, McCabe score: 1 (36 ;%), 2 (31 ;%), 3 (25 ;%), Winston score≤2 in 67 ;%	CR	In-hospital mortality. All combo[b]: 37; 27 ;% tige+rif+ami: 9; 33.3 ;% sulb+ami: 8; 25 ;% coli+rif: 1; 0 ;% tige+coli+rif: 19; 26.3 ;%	In-hospital mortality. All mono[b]: 33; 63.6 ;% tige: 11; 81.8 ;% sulb: 6; 66.7 ;% ami: 8; 37.5 ;% tobra: 4;	NR	NR	NR	NR	2 pts with bacteremia on tige mono developed resistance	Risk factors for mortality among pts with adequate definitive treatment: McCabe 1 and monotherapy vs. combination treatment

Table 1 (continued)

First author, year	Study period	Study design	Number of pts; site of infection	Patient characteristics; co-morbidity	*Acinetobacter* susceptibility pattern	Antibiotic treatment (*n*); mortality (%)		Statistical analyses on mortality	Clinical success (%) (combo vs. mono)	Eradication (%) (combo vs. mono)	Adverse events (%) (combo vs. mono)	Emergence of resistance (combo. vs. mono.)	Comments
						Combination	Monotherapy						
			catheter, 34 SSTI, 5 IAI				75 ;% coli: 4; 50 ;%						
Kuo, 2007 [19]	2003–2005	Retrospective	55 (treatment data available for 48); BSI	83 ;% ICU patients; mean age: 62 years, 41 ;% septic shock	PDR[c]	30-day. All combo: 36; 36.1 ;% carba+asm: 26; 30.8 ;% carba+ami: 10; 50 ;%	30-day. Carba: 12; 58.3 ;%	NR	NR	NR	NR	NR	Lower mortality for carba+asm (p=0.01)
Lee, 2005 [26]	2000–2002	Retrospective	89; source of isolation: 61 sputum, 11 wound, 15 urine, 1 blood, 1 CSF	Mean age: 70.6 years; APACHE II scores were lower in carba-sulb-treated pts	Majority PDR[d]	Carba+sulb: 59; 40.7 ;% AG+ (2nd/3rd cephalosporin, or antipseudomonal penicillin, or fluoroquinolone): 30; 43.3 ;%	NA	No sig. difference between carba+sulb and the others	42.4 ;% (carba+sulb) vs. 40 ;% (others), p=NS	35.6 ;% (carba+sulb) vs. 46.7 ;% (others)	None	NR	No
Lim, 2011 [20]	2000–2007	Retrospective	70 (treatment data available for 31); BSI, site of entry: 25 pneumonia, 37 IAI, 1 UTI, 3 CVC, 1 SSTI, 3 primary	Inpatients APACHE II score (median) 20. Age, years (median): 56 coli group, 54 non-coli group	Colistin group XDR (COS[e])	30-day. All combo[f]: 11; 45.5 ;%	30-day. Coli: 20; 30 ;%	No sig. difference between coli and non-coli, or coli combo and coli mono	NR	NR	Renal dysfunction: 50 ;% (coli) vs. 28.6 ;% (non-coli) p=NS	NR	APACHE II≥21 was a predictor of mortality in the total population (both coli- and non-coli-treated)
Oliveira, 2008 [15]	1996–2004	Retrospective	167; 78 primary BSI, 53 pneumonia, 29 SSI, 7 other	87.4 ;% ICU admission; median age (years) (polymixins): 63 (8–87), (asm) 54 (7–89), median APACHE II score (polymixins): 15 (3–39), (asm) 16 (1–50)	CR[g]	Polymixins group: concomitant use of carba (29 ;%), vanco (70 ;%), AG (2 ;%). Asm group: concomitant use of carba (28 ;%), vanco (60 ;%), AG (4 ;%)	Polymixins: 82; 76.8 ;% (in-hospital), 50 ;% (during treatment). Asm: 85; 63.5 ;% (in-hospital), 32.9 ;% (during treatment)	Higher mortality during treatment in the polymixins group (p=0.03). No sig. difference in in-hospital mortality between the two arms	NR	NR	Renal failure in 26 ;% of each arm. Skin rash: 4 ;% (polymixins group), 13 ;% (asm)	NR	Risk factors for: (1) mortality during treatment: treatment with polymyxins, APACHE II≥15, septic shock, delay>48 ;h in starting treatment, renal failure; (2) in-hospital mortality: age≥58 years, APACHE II≥15, septic shock
Shields, 2012 [18]	2006–2011	Retrospective	41 (37 clinically evaluable); 36 VAP, 1 HAP, 3 VAT, 1 bacteremia	SOT, median age years: 56 (21–80), median APACHE II score: 19 (8–	XDR	28-day. All combo[h]: 33 (33.3 ;%)	28-day: All mono[h]: 4; 100 ;%	Lower mortality with combination than with monotherapy (p=0.03). Coli+carba	54.5 ;% combination therapy vs. 0 ;% monotherapy. Coli+carba 76 ;% (16/21)	NR	NR	Colistin resistance in 36 ;%. Coli+carba was associated with lower	Clinical success was higher when colistin was combined with a carbapenem versus other agents (76 ;% vs. 9 ;%; p=0.0005)

Table 1 (continued)

First author, year	Study period	Study design	Number of pts; site of infection	Patient characteristics; co-morbidity	*Acinetobacter* susceptibility pattern	Antibiotic treatment (*n*); mortality (%)		Statistical analyses on mortality	Clinical success (%) (combo vs. mono)	Eradication (%) (combo vs. mono)	Adverse events (%) (combo vs. mono)	Emergence of resistance (combo. vs. mono.)	Comments
						Combination	Monotherapy						
				29), 98 ;% ICU patients				was associated with survival (multivariate analysis: OR=7.88, 95 ;% CI: 1.60–38.76)	better than other combinations 9 ;% (1/11) (p=0.0005)			resistance than coli+ tige (p=0.03)	
Tasbakan, 2011 [22]	2009–2011	Retrospective	72; 25 HAP, 47 VAP	Inpatients (part of whom were ICU patients); mean APACHE II score: (mono) 19.6 ±5.2, (combo) 19.3±5.6, mean age 65.9 years	At least[i] MDR, 23 XDR (only tige susceptible)	30-day. All tige combinations: all[j]: 49; 57.1 ;%	30-day. Tige: 23; 52.2 ;%	No sig. difference between the two arms	NR	67.3 ;% vs. 60.9 ;%, p=NS	NR	NR	Higher eradication in pts with lower mean APACHE II score (p=0.001)
Tseng, 2007 [16]	2001–2004	Retrospective	56; bacteremia	Inpatients, 69.6 ;% in the ICU; mean age: 65.5±16 years, mean APACHE II score: 20.8± 9.3	PDR[c]	30-day. Regimes containing carba+asm±AG: 9; 44.4 ;% carba+AG±asm: 19; 52.6 ;%	30-day. Regimes containing Asm: 22; 40.9 ;%	No sig. difference between the treatment regimens	NR	NR	NR	NR	Pitt bacteremia score ≥4 and presence of immunosuppression were independent predictors for mortality
Ye, 2011 [23]	2007–2010	Retrospective	112 (116 episodes); RTI (mostly VAP); multi-site infections in 44.8 ;%	Mean age: 70.8± 15.5 years, mean APACHE II score: 21.7± 6.6	MDR	30-day. All tige combinations[k]: 72; 43.1 ;% tige+coli: 20; 50 ;% tige+ CEPH: 29; 34.5 ;% tige+ sulb: 9; 55.6 ;% tige+ carba: 11; 72.7 ;% tige+ AG: 9; 44.4 ;% tige+FQ: 16; 37.5 ;%	30-day. Tige: 44; 25 ;%	Tige combinations were not associated with 30-day mortality in multivariate analysis	61.1 ;% (combo)[k] vs. 59.1 ;% (mono), p= NS	Overall: 32.7 ;%	NR	Tigecycline resistance during treatment in 24.6 ;%	Independent predictors of failure of clinical resolution: higher APACHE II score, bilateral pneumonia, monomicrobial pneumonia, and female gender. Independent predictor of mortality: deterioration of pneumonia on chest radiographs

tige tigecycline, *coli* colistin, *asm* ampicillin/sulbactam, *sulb* sulbactam, *rif* rifampicin, *carba* carbapenem, *imi/cil* imipenem/cilastatin, *ami* amikacin, *tobra* tobramycin, *czd* ceftazidime, *cfpm* cefepime, *vanco* vancomycin, *cipro* ciprofloxacin, *levo* levofloxacin, *ceph* cephalosporin, *FQ* fluoroquinolone, *AG* aminoglycoside, *cfpz* cefoperazone, *NR* not reported, *NA* not applicable, *RCT* randomized controlled trial, *pts* patients, *mono* monotherapy, *combo* combination, *BSI* bloodstream infections, *IAI* intra-abdominal infection, *SSI* surgical site infection, *ICU* intensive care unit, *UTI* urinary tract infection, *SSTI* skin and soft tissue infection, *RTI* respiratory tract infection, *VAP* ventilator-associated pneumonia, *VAT* ventilator-associated tracheobronchitis, *HAP* hospital-acquired pneumonia, *CVC*

central venous catheter, *CSF* cerebrospinal fluid, *CNS* central nervous system, *XDR* extensively drug-resistant, *MDR* multidrug-resistant, *PDR* pandrug-resistant, *CR* carbapenem-resistant, *COS* colistin-only susceptible, *sig.* significant, *NS* non-significant, *OR* odds ratio, *CI* confidence interval, *HR* hazard ratio, *APACHE* Acute Physiology and Chronic Health Evaluation, *SAPS* Simplified Acute Physiology Score, *SOT* solid organ transplant

[a] Asm was administered 9 ;g q8h

[b] Definitive treatment was not adequate in 20 patients. Among them, seven patients did not receive antibiotic treatment and died

[c] Tigecycline, colistin, doxycycline, and sulbactam were not tested

[d] Tigecycline and colistin were not tested

[e] Tigecycline was not tested. In the non-colistin group, 17 isolates were COS; the others were not tested for colistin and tigecycline but were resistant to all other drugs, including sulbactam

[f] Colistin combination regimens: coli+carba: 7, coli+asm or cfpz/sulb: 3, unknown combination: 1

[g] Colistin was not tested

[h] Combination regimens: coli+tige: 1, coli+tige+rif: 2, coli+tige+ami: 1, coli+tige+asm: 1, coli+rif: 1, coli+cfpm: 1, coli+asm: 4, coli+carba: 15, coli+carba+tige: 2, coli+carba+rif: 1, coli+carba+asm: 3. Monotherapy regimens: carba: 2, 100 ;%; tige: 1, 100 ;%; cfpm: 1, 100 ;%

[i] All isolates were at least tigecycline-susceptible, but colistin was not tested

[j] Tigecycline combination regimens: tige+cfpz+sulb: 26, tige+ntl: 13, tige+ami: 3

[k] Some patients received more than one antibiotic with tigecycline during an infectious episode

Many in vitro and in vivo studies have explored the possible synergy of antibiotics in order to overcome *Acinetobacter* resistance. Such combinations include carbapenems with sulbactam [7] or aminoglycosides [8] or rifampicin [9], as well as polymyxins with rifampicin or carbapenems [10] and sulbactam with fosfomycin [11]. However, the results from in vitro and in vivo studies cannot always be translated into clinical practice.

In this context, we aimed to search the published evidence and address the matter of optimal treatment for *Acinetobacter* spp. infections focusing on MDR, XDR, and PDR strains.

Methods

Literature search

A systematic search was performed in the PubMed and Scopus databases by two independent investigators (P.P. and G.S.T.). The following search term was applied to the PubMed database: "(acinetobacter or baumannii or non-fermenting or non fermentative)" AND (treatment) AND (multidrug-resistant OR extensively drug-resistant OR pandrug-resistant OR XDR OR PDR OR MDR). A more conservative term was applied in the Scopus database: (acinetobacter) AND (treatment) AND (drug-resistant OR xdr OR pdr OR mdr). The bibliographies of all eligible studies were hand-searched in an effort to identify additional potentially eligible studies. Only articles published in English, German, French, Spanish, Italian, or Greek were evaluated.

Inclusion criteria

Eligible studies should include at least ten patients and be comparative with regard to the antibiotic treatment against MDR, XDR, and PDR *Acinetobacter* spp. Also, *Acinetobacter* spp. in the studies should be isolated from specimens of any origin, as long as they were the causative pathogens of the clinical infections studied. We only included studies that performed statistical analysis evaluating the outcomes of *Acinetobacter* spp. infection with regard to the administered treatment. Comparison between treatment regimens could be between monotherapy and combination therapy, between combination therapies, or between monotherapies. We also included studies that compared different antibiotics, providing the concomitant antibiotics used were the same between the two arms. We included only studies using intravenous administration of antibiotics.

Exclusion criteria

Microbiological (in vitro) or in vivo studies were excluded. Studies on patients colonized but not infected by

Acinetobacter spp. were excluded. Studies on neonates, pediatric, or pregnant population were also excluded. Studies comparing mixed regimens, as well as studies examining the benefit of other than the intravenous route of administration, were not included.

Definitions and outcomes

MDR, XDR, and PDR *Acinetobacter* spp. definitions are in accordance with the international expert proposal for interim standard definitions for acquired resistance [12]. Thereby, MDR was defined as non-susceptibility to at least one agent in three or more antimicrobial categories approved for the treatment of *Acinetobacter* spp. infection, XDR was defined as non-susceptibility to at least one agent in all but two or fewer antimicrobial categories, and PDR was defined as non-susceptibility to all agents in all antimicrobial categories. We applied the aforementioned definition for the antimicrobial categories tested in each study, including tigecycline where applicable. The administration of sulbactam is commonly accompanied by ampicillin, since, in most countries, the only available preparation of sulbactam is within a fixed combination of ampicillin/sulbactam. Sulbactam alone has been found to have intrinsic activity against *Acinetobacter* spp. [13], and it has been suggested that the activity of ampicillin/sulbactam against *Acinetobacter* spp. is exclusively due to sulbactam [14]. Thus, we included ampicillin/sulbactam in the monotherapy arm.

The primary outcome was 28-day or 30-day mortality. If this type of mortality was not recorded, other types of mortality were extracted. Secondary outcomes included clinical success, microbiological eradication, emergence of resistance, and adverse events.

Results

Twelve studies were included, reporting on 1,040 patients (1,044 episodes) with infection due to MDR *Acinetobacter* spp., and their characteristics are presented in Table 1. The study selection process is depicted in Fig. 1. Combination therapy and monotherapy was implemented in 431 and 333 episodes of infection, respectively, while in 223 episodes, the type of therapy could not be identified [15, 16]. Of the remaining 57 episodes of infection, no treatment was administered in 11 episodes [17, 18], and treatment data were not available for 46 episodes [19, 20]. Seven studies [17–23] compared combination treatment with monotherapy. Two studies compared monotherapy regimens [24, 25], one compared combination treatments [26], and one compared polymyxins (B and E) and ampicillin/sulbactam with and without combination treatment [15]. Finally, one study explored the benefit of ampicillin/sulbactam or carbapenems with ampicillin/sulbactam or carbapenems with aminoglycosides within the treatment regimens in patients mostly receiving combination treatment [16].

Treatment regimens consisted of colistin and colistin-based combinations in two studies [20, 21], tigecycline and tigecycline-based combinations in two studies [22, 23], mostly carbapenem-based combinations in two studies [16, 26], and treatment regimens that included carbapenems, sulbactam, tigecycline, polymyxins, cephalosporins, rifampicin, and aminoglycosides in the remaining six studies [15, 17–19, 24, 25].

Mortality

The overall mortality between studies varied from 28.6 % [24] to 70 % [15]. The 28-day or 30-day mortality for the eight studies [16, 18–24] that reported the respective results varied from 28.6 % [24] to 55.5 % [22], while the in-hospital [15, 17, 25] and overall mortality [26] in the remaining four studies varied from 39 % [25] to 70 % [15]. The mortality of the monotherapy arm between studies varied from 25 % (11/44 patients) [23] with tigecycline to 100 % (4/4 patients) [18] with tigecycline, carbapenem, and cefepime monotherapy. Among the different monotherapy regimens, the lowest mortality (23.1 %; 3/13 patients) was achieved with high doses of ampicillin/sulbactam [24].

The mortality of patients receiving combination treatment varied from 27 % (10/37 patients) [17] with various combinations that included tigecycline, colistin, rifampicin, and sulbactam to 57.1 % (28/49 patients) [22] with tigecycline-based combinations. Combination treatment regimens were superior in terms of survival in three studies [17–19], while four studies found no significant differences between combination treatment and monotherapy [20–23]. Among the studies that favored the combination treatment, carbapenem either with colistin (mortality 19 %; 4/21 patients, $p=0.009$) [18] or with ampicillin/sulbactam (mortality 30.8 %; 8/26 patients, $p=0.012$) [19], and overall combination treatment that included tigecycline-, colistin-, or sulbactam-based combinations (mortality 27 %, 10/27 patients, $p<0.05$) [17] were the regimens that showed the greatest benefit. With regard to studies that found no benefit from combination regimens, two compared between tigecycline alone or in combination with other antibiotics [22, 23] and two compared colistin alone or in combination with other antibiotics [20, 21]. In one study [23], tigecycline combinations, particularly with carbapenems, were associated with high mortality in the univariate analysis; however, this was not confirmed in the multivariate analysis.

One study examined only combination treatments and did not find a difference in mortality between carbapenem with sulbactam and aminoglycoside-based regimens [26] (41 % vs. 43 %, $p\geq0.05$). One additional study found no benefit from

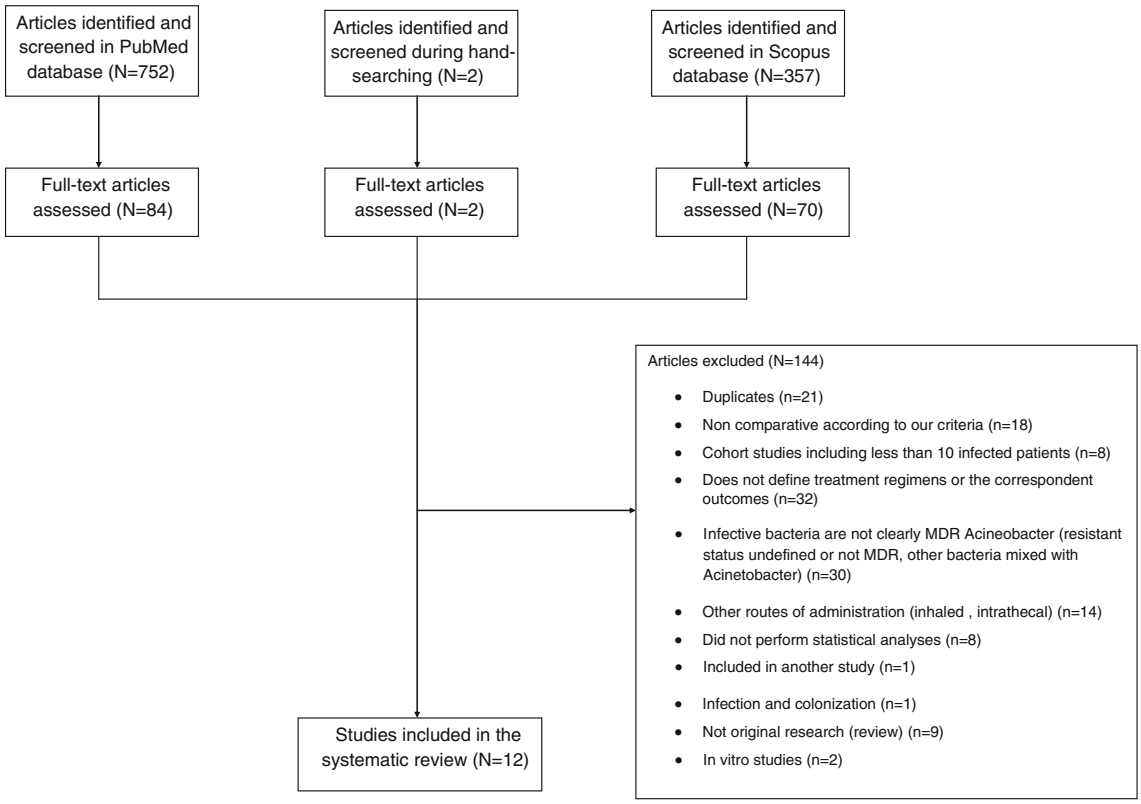

Fig. 1 Flow diagram of the systematic search and selection of studies for inclusion in the review

carbapenem with ampicillin/sulbactam (mortality 44.4 %, p= 0.805), or carbapenem with an aminoglycoside (mortality 52.6 %, p=0.635), or ampicillin/sulbactam (mortality 40.9 %, p=0.38) in the treatment regimens (monotherapy or combination treatment) [16].

Among the studies that compared monotherapy regimens, colistin in comparison to tobramycin was associated with in-hospital (50 % vs. 28.1 %, p=0.04) but not ICU mortality (34.4 % vs. 21.9 %, p =0.75) in predominantly respiratory tract infections [25]. Another study [24] compared colistin and high doses of ampicillin/sulbactam monotherapy and found no significant difference in mortality (33.3 % vs. 23.1 %, $p\geq$ 0.05).

Finally, one study that compared polymyxins with ampicillin/sulbactam, either as monotherapy or combined with a carbapenem or vancomycin, or aminoglycosides, showed that polymixins were independently associated with during-treatment mortality [odds ratio (OR): 2.07; 95 % confidence interval (CI): 1.03 to 4.16, p=0.041] but not in-hospital mortality [15].

Clinical success

Among four studies [18, 23, 24, 26] that reported relevant data, clinical success or resolution varied between 42 % [26] with aminoglycoside-based combinations and 61.5 % [24] with ampicillin/sulbactam monotherapy. One study showed that colistin combination with carbapenems was associated with clinical success (76 %, p = 0.0002) compared to other monotherapy or combination regimens [18]. Two studies did not find significant differences in the clinical success between carbapenem with sulbactam and aminoglycoside-based combinations (42.4 % vs. 40 %, $p\geq$0.05) [26] and between colistin and high-dose ampicillin/sulbactam monotherapy (60 % vs. 61 %, $p\geq$0.05) [24], respectively. One study [23] compared tigecycline-based combination treatment and tigecycline monotherapy and found no difference in clinical resolution (61.1 % vs. 59.1 %, p=0.83).

Microbiological eradication and emergence of resistance

Microbiological eradication among six studies that provided relevant data [21–26] varied from 32.7 % [23] to 67.3 % [22]. No significant difference was found between carbapenems with sulbactam and aminoglycoside-based combinations (35.6 % vs. 46.7 %, $p\geq$0.05) [26], or between tobramycin and colistin monotherapy (55 % vs. 50 %, $p\geq$0.05) [25] in two studies. One study [22] compared tigecycline-based combinations and tigecycline monotherapy and also found no difference in eradication (67.3 % vs. 60.9 %, $p\geq$0.05). Another study [24] found no difference between colistin and high-dose ampicillin/sulbactam monotherapy on bacteriological success (66.6 % vs. 61.5 %, $p\geq$0.05). In one study [21], eradication was associated with the combination of colistin with

rifampicin compared to colistin monotherapy (60.6 % vs. 44.8 %, p=0.034). Lastly, one study reported only on the overall eradication (32.7 %) [23].

Four studies reported on the emergence of resistance [17, 18, 21, 23]. One study [21] reported on colistin alone or in combination with rifampicin and did not find the emergence of resistance. In one study [17], the emergence of tigecycline resistance occurred in two patients suffering from bacteremia with tigecycline monotherapy (18.2 %) and in one study with tigecycline monotherapy and combination therapy [23], the emergence of tigecycline resistance occurred in 28 episodes of respiratory tract infection (24.6 %). Finally, one study with predominantly colistin-based combinations found the emergence of resistance in five patients (36 %) [18] in mostly respiratory tract infections. However, the colistin–tigecycline combination resulted in significantly more episodes of emergence of resistance than colistin with carbapenems (3 patients, 100 % vs. 2 patients, 18.2 %, p=0.03).

Adverse events

Six studies [15, 20, 21, 24–26] provided data on adverse events. Nephrotoxicity in patients treated with polymyxins [15, 20, 21, 24, 25] varied from 19 % [25] to 50 % [20] and was higher than the comparative antibiotics in most studies [20, 24, 25]. However, colistin was not significantly associated with nephrotoxicity in comparison to tobramycin [25], high-dose ampicillin/sulbactam [24], or treatment regimens that included carbapenems, fluoroquinolones, piperacillin–tazobactam, and sulbactam alone or in combinations [20]. In the study that compared polymyxins (B and E) with ampicillin/sulbactam alone or in combination with carbapenems or aminoglycosides [15], nephrotoxicity occurred in 26 % of patients in each treatment arm, respectively. The same study reported on skin rashes in three patients (4 %) in the polymyxins arm and 11 patients (13 %) in the ampicillin/sulbactam arm. Solitary episodes of skin rash and diarrhea were observed in patients receiving high-dose ampicillin/sulbactam [24]. In the study [26] in which patients received carbapenems with ampicillin/sulbactam or aminoglycoside-based combinations, no adverse events were observed. Finally, only one study [21] compared the incidence of adverse events between combination treatment and monotherapy (colistin with rifampicin and colistin, respectively) and showed a non-significant trend of hepatotoxicity in the former arm (20.8 % vs. 11.9 %, p=0.13). Notably, neurotoxicity was observed in only one of the patients that received polymyxins [21].

Discussion

This systematic review aimed to assess the available evidence on combination treatment and monotherapy against MDR *Acinetobacter* spp. Combination treatment was superior to monotherapy with regard to mortality in three studies; however, these results were not validated in the other studies of the review. Additionally, most studies had small sample sizes and were retrospective in nature. Thus, we did not find robust evidence that would lead to a firm recommendation.

The high rates of mortality noted are in accordance with previous studies in which the mortality of *Acinetobacter* spp. infections was between 26 and 61 % [27]. The lowest overall mortality among patients that received monotherapy was achieved with high-dose ampicillin/sulbactam monotherapy (23.1 %) [24] in ampicillin/sulbactam-resistant *Acinetobacter* spp. Sulbactam exhibits activity against *Acinetobacter* spp. by directly binding to penicillin-binding proteins [13]. The current in vitro susceptibility testing for ampicillin/sulbactam may not directly translate into the clinical effectiveness of sulbactam [28, 29]. Furthermore, high doses of sulbactam may prolong the time above the minimum inhibitory concentration (MIC) that has been shown in vivo to achieve better therapeutic results [30]. Despite the fact that the study [24] was conducted among patients with the lowest APACHE II score (mean: 14), which may justify the low mortality, ampicillin/sulbactam was found to be equally effective with colistin against colistin-susceptible strains, while Oliveira et al. [15] found that ampicillin/sulbactam, both as monotherapy and combined with carbapenems or aminoglycosides, led to lower during-treatment mortality than polymyxins. Other studies that did not include MDR *Acinetobacter* strains exclusively found equal effectiveness of ampicillin/sulbactam and imipenem/cilastatin [31]. These data support the use of ampicillin/sulbactam against MDR *Acinetobacter* spp. and emphasize the need for further research on the MIC breakpoints and administration strategies (i.e., higher dose, extended infusion) of sulbactam.

Combination treatment is currently preferred in serious infections caused by Gram-negative MDR organisms [32], especially *Pseudomonas* and *Acinetobacter* spp. [33], while studies suggest that combination treatment may benefit patients with bacteremia from KPC-producing *Klebsiella pneumoniae* [34]. However, combination treatment has been questioned, even in infections where it has been a long-standing common practice, like in bacterial endocarditis [35]. Moreover, if there is no benefit from combination treatment, then the burden of possible additional adverse events is not justified. Two meta-analyses addressed the issue of beta-lactam monotherapy or combined with aminoglycosides and found no difference in the mortality or emergence of resistance between the compared treatments [36, 37], and one noted an increased incidence of adverse events with combination treatment [37]. One additional meta-analyses [38] compared monotherapy or combination treatment for *P. aeruginosa* infections in particular and also found no

difference in the mortality. In our review, three studies showed benefit from combination treatment [17–19].

The first study that favored combination treatment [17] used colistin with rifampicin, sulbactam with aminoglycosides, tigecycline with colistin and rifampicin, and tigecycline with rifampicin and amikacin, all administered based on susceptibility, with the exception of rifampicin, which was not tested. Notably, this study did not provide regimen administration by site of infection that could confound the comparison of combination treatment and monotherapy. Tigecycline alone or combined with other antibiotics may have been more effective in skin and soft tissue infections and less effective in hospital-acquired pneumonia [39], while aminoglycoside monotherapy may not have been effective in infections other than those of the urinary tract [40, 41]. Additionally, another study [22] that also administered antibiotics based on susceptibility found no differences in mortality between tigecycline monotherapy and combined with cefoperazone/sulbactam or aminoglycosides. However, the most frequently administered combination of tigecycline with colistin and rifampicin in the study by Hernandez et al. was not employed in the former study. Also, a synergistic effect between tigecycline with colistin, tigecycline with rifampicin, and colistin with rifampicin, as has been suggested by in vitro studies [42, 43], cannot be excluded.

The second study [18] which reported on respiratory tract infections due to colistin- and tigecycline-only susceptible *Acinetobacter* strains showed that the carbapenem–colistin combination was superior to non-colistin monotherapy and other combinations that included colistin. This could be attributed to a synergistic effect of this combination, as has been suggested by in vitro studies [44]. On the other hand, colistin with carbapenems was the most commonly administered regimen in an overall small sample of patients (27 in 36 patients). Also, these findings are juxtaposed to the findings of another study [20] that found no superiority of colistin-based combination treatment (mostly with carbapenems) in patients with bacteremia mainly secondary to intra-abdominal infections.

The third study that favored the carbapenem–sulbactam combination [19] included patients with bacteremia caused by carbapenem-resistant *Acinetobacter*. The carbapenem–sulbactam combination was administered for carbapenem-resistant *Acinetobacter* in three studies overall [16, 19, 26], but the remaining two studies [16, 26] found no benefit from this combination. Different susceptibilities in sulbactam may account for this discrepancy, since susceptibility to sulbactam was tested in only one of the studies [26]. Notably, in the latter study [26], the synergy of carbapenem with sulbactam against resistant *Acinetobacter* spp. was documented in vitro; however, this did not translate to clinical effectiveness. In all three studies, *Acinetobacter* spp. were considered PDR; however, tigecycline and colistin were neither tested for susceptibility nor administered.

Severity of illness was an independent predictor of mortality in four studies [15–17, 20]. Among eight studies that provided data on the APACHE II score [15, 16, 18, 20, 22–25], mortality did not correlate consistently with higher APACHE II scores. The APACHE II score, even though it is a useful tool, has been questioned on its ability to accurately predict mortality [45–47]. Nonetheless, predominantly monotherapy with polymyxins or ampicillin/sulbactam resulted in the highest in-hospital mortality among patients with bacteremia and low APACHE II score (median score: 15–16, mortality 70 %) [15]. However, in another study [20] reporting on patients with bacteremia and higher APACHE II score (median: 20), the 30-day mortality with colistin monotherapy was only 30 %. The carbapenem–colistin combination resulted in rather lower mortality than other treatment regimens with regard to the severity of disease, and this may be the result of synergy, as has been suggested [18]. Rather low mortality relative to the severity of disease was observed in two other studies [20, 23]; however, the mortality of each study was not significantly different between the compared arms and, thus, we cannot make assumptions on the contribution of the individual antibiotic treatment in these discrepancies.

Overall, adverse events referred mainly to nephrotoxicity in patients receiving polymyxins. Only one study compared the incidence of adverse events between monotherapy and combination treatment [21] (colistin and colistin with rifampicin, respectively) and found no significant difference. Nephrotoxicity with polymyxins was not significantly higher compared to other antibiotics in the studies that provided the relevant data, confirming that polymyxins are generally safe antibiotics [48]. Tigecycline monotherapy or in combination with other antibiotics was most commonly involved in cases of emergence of resistance during treatment. This may account for the fact that tigecycline was administered for off-label uses (bloodstream infections and respiratory tract infections, most probably hospital-acquired). It has been suggested that suboptimal concentrations of tigecycline at the site of infection [49, 50] with the traditional dosing scheme may account for the poor performance of tigecycline in off-label uses, and this could also explain the emergence of resistance. Notably, only four studies reported on the emergence of resistance, and three of them used tigecycline in their treatment regimens.

The effect of the implemented treatment on clinical success and microbiological eradication were generally in accordance with the effect on survival, with the exception of the study that found colistin and rifampicin to be superior to colistin monotherapy in microbiological eradication but not survival [21]. Additionally, another study found that clinical resolution was significantly higher in polymicrobial than in monomicrobial infections [23]. The contribution of *Acinetobacter* spp. in the clinical severity of the critically ill patient is difficult to determine [51]. Inconsistency between microbiological eradication

and clinical success may reflect that the clinical severity of these patients was not attributed mainly to *Acinetobacter* spp. This supports the argument that combination treatment may prove beneficial by broadening the antimicrobial spectrum in severely ill patients.

Our results should be interpreted in view of many limitations. The great majority of the included studies had a non-randomized, retrospective study design and included small numbers of patients. The lack of randomized controlled trials and the great heterogeneity between studies precluded the conduct of a meta-analysis and the drawing of more robust conclusions. Also, there were differences in definitions between studies with regard to mortality, nephrotoxicity, resistance pattern, susceptibility testing methods, dosing regimens, and population studied. Only a few studies provided data on the secondary outcomes of clinical success, adverse events, microbiological eradication, and the emergence of resistance.

In conclusion, combination antibiotic treatment was found to be superior to monotherapy in three studies with severely ill patients (mainly ICU patients). However, limitations of the studies as well as other studies that juxtapose the results preclude a firm recommendation. The contribution of *Acinetobacter* spp. in critically ill patients where the infection may be polymicrobial is difficult to determine and, thus, it seems reasonable for the time being that combination treatment may benefit severely ill patients. Randomized controlled trials using uniform protocols should be performed urgently to provide solid evidence with regard to the effectiveness of combination therapy and monotherapy in *Acinetobacter* spp. infections.

Conflict of interest None.

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