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Review

Therapeutic options for *Burkholderia cepacia* infections beyond co-trimoxazole: a systematic review of the clinical evidence

Sophia G. Avgeri[a], Dimitrios K. Matthaiou[a], George Dimopoulos[a,b], Alexandros P. Grammatikos[c], Matthew E. Falagas[a,d,e,*]

[a] *Alfa Institute of Biomedical Sciences (AIBS), 9 Neapoleos Street, 151 23 Marousi, Athens, Greece*
[b] *Department of Critical Care, University Hospital 'Attikon', Medical School, University of Athens, Greece*
[c] *Department of Medicine, 'G. Gennimatas' Hospital, Thessaloniki, Greece*
[d] *Department of Medicine, Tufts University School of Medicine, Boston, MA, USA*
[e] *Department of Medicine, Henry Dunant Hospital, Athens, Greece*

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ABSTRACT

Burkholderia cepacia complex (BCC) is an important group of pathogens affecting patients with cystic fibrosis and chronic granulomatous disease as well as immunocompromised and hospitalised patients. Therapeutic options are limited owing to high levels of resistance of the organism, either intrinsic or acquired, to many antimicrobial agents. Co-trimoxazole (trimethoprim/sulfamethoxazole) has been a drug of choice. However, in some cases it cannot be administered because of allergic or hypersensitivity reactions, intolerance or resistance. We systematically searched for relevant publications including clinical data in PubMed and Scopus. The search identified 48 relevant case reports (57 cases) and 8 cohort studies or trials. Nineteen (33.3%) of 57 patients included in the case reports received ceftazidime-based regimens, 14 (73.7%) of whom were cured. Meropenem was administered in seven patients (12.3%), one (14.3%) of whom improved and five (71.4%) were cured. Seven (12.3%) of 57 cases were treated with penicillins, four of which were piperacillin (all had a favourable outcome). Based on the data reported in the eight relevant cohort studies or trials identified, favourable outcomes were observed in 68.4% (26/38) to 100% (16/16) of cases treated with ceftazidime and 66.7% (6/9) of cases treated with meropenem. Also, 9/12 (75%) of patients receiving penicillins improved. Thus, Ceftazidime, meropenem and penicillins, mainly piperacillin, either alone or in combination with other antimicrobial agents, may be considered as alternative options for BCC infections, according to the in vitro antimicrobial susceptibility patterns and clinical results. However, the available clinical data are not sufficient and further clinical experience is required to clarify the appropriateness of these antibiotics for BCC infections.

1. Introduction

Burkholderia cepacia, formerly known as *Pseudomonas cepacia*, is an aerobic, glucose-non-fermenting, Gram-negative bacillus that can develop under conditions of minimal nutrition and is resistant to the action of certain disinfectants [1,2]. It was first described by Burkholder in 1950 as a phytopathogen of the onion bulb [3].

Burkholderia cepacia has been recognised as a group of highly virulent organisms known as *B. cepacia* complex (BCC), which is associated mainly with infections in patients with cystic fibrosis (CF) and chronic granulomatous disease (CGD) [4–6] as well as in immunocompromised and hospitalised patients [7,8]. There have also been reports documenting BCC as being responsible for endocarditis in drug addicts [9] or patients with prosthetic heart valves [10], eye infections following surgery [11,12] and infections or abscesses of the central nervous system [13–15].

As far as CF patients are concerned, although *Pseudomonas aeruginosa* is the most common pathogen of their lower airways, BCC has also been detected along with other new emergent pathogens such as *Stenotrophomonas maltophilia* and *Alcaligenes xylosoxidans* [5,16–18]. *Burkholderia cenocepacia* and *Burkholderia multivorans* are the most common genomovars isolated from patients with CF. *Burkholderia cepacia* can be a chronic coloniser in these patients and can also cause acute exacerbations when more virulent genotypes replace the already existent strains [5,19]. This is a fact of great importance, as the main characteristic of CF is chronic pulmonary infections complicated by acute exacerbations requiring antimicrobial treatment, and the greatest proportion of

* Corresponding author. Tel.: +30 210 683 9604; fax: +30 210 683 9605.
E-mail address: m.falagas@aibs.gr (M.E. Falagas).

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deaths (90%) in these patients are ascribed to loss of lung function [20].

Therapeutic options for BCC are unfortunately limited because many strains of the organism exhibit high levels of resistance to many antimicrobial agents in vitro, which may be intrinsic for certain classes [21–23]. There are studies reporting up to 50.4% resistance to every antibiotic tested, indicating that multidrug-resistant isolates are not at all uncommon [24].

The antimicrobial option most commonly used in BCC infections is co-trimoxazole (trimethoprim/sulfamethoxazole) [25–31]. Co-trimoxazole has also been considered as the prophylactic drug of choice for CGD [32,33]. However, allergic or hypersensitivity reactions, intolerance and resistance may be observed in patients receiving co-trimoxazole [34]. We sought to review the literature critically in order to identify treatments other than co-trimoxazole that can be administered alternatively in patients with BCC infections.

2. Literature search

A systematic review of the literature was performed to investigate alternative therapeutic options for BCC infections except for co-trimoxazole. Two investigators (SGA and APG) independently searched PubMed and Scopus up to February 2008 using the search terms '*Burkholderia cepacia*' OR '*Pseudomonas cepacia*'. An additional search was performed manually of the reference lists of the retrieved studies.

3. Study selection and data extraction

An article was considered eligible if it included patients with a BCC infection treated with systemic antibiotics other than co-trimoxazole to which isolates were not resistant and the outcome of treatment was reported. If the antimicrobial regimen comprised a combination of antibiotics, one of which was co-trimoxazole, or if the administration was only topical, the article was excluded. Articles reporting data of either colonised patients without an acute infection or post-mortem isolation of the pathogen, as well as animal studies, were excluded. Conference abstracts and studies published in languages other than English, French, Spanish, German, Italian or Greek were not included in the review.

Data extracted and tabulated from each case report were: author name; year of publication; patient sex; age; co-morbidity; type of infection; administered antibiotic; and infection outcome. Additionally, from case series, retrospective or prospective studies and randomised clinical trials, data regarding the number of evaluable patients, isolates and treatment courses were retrieved. When patients fulfilling the aforementioned inclusion criteria were a subset of the study population, only data referring to these patients were extracted, if available.

4. Definitions

The outcome of infection was evaluated as cure, improvement or failure according to the definitions provided by each individual study. Failure was defined as either death of the patient or sequelae, when either of them was attributed to the infection.

5. Available clinical evidence

The process of retrieval and selection of the included articles is depicted in detail in Fig. 1. The total numbers of studies identified in the PubMed and Scopus databases were 2211 and 752, respectively. As 2907 studies were excluded for various reasons, 56 studies were considered eligible for this review and are presented in Tables 1 and 2.

5.1. Case reports

The main characteristics of the retrieved case reports are described in Table 1. Forty-eight case reports [4,11–15,35–76] presenting 57 cases were included; 36 (64.3%) of 56 patients were men, whilst sex was not reported in 1 case. The median age of the included patients was 35 years (range 0–78 years). Seven (12.3%) of the 57 patients suffered from CF [14,39,42,50,60,67,74] and 5 (8.8%) suffered from CGD [4,46,66].

Nineteen (33.3%) of 57 patients received ceftazidime; 10 (52.6%) received it as monotherapy [35,36,44,47,48,51,56,57,70] and 9 (47.4%) in combination with other antimicrobial agents, which was piperacillin in 2 cases [13,52] and levofloxacin [53], ciprofloxacin [15], tobramycin [73], imipenem [48], aztreonam/lincomycin [67], vancomycin (intravitreal/topical treatment) [11] and vancomycin/metronidazole/chloramphenicol [14] in 1 case each. All of the ceftazidime monotherapy recipients were cured. In total, 14 (73.7%) of 19 patients receiving ceftazidime-based regimens were cured. One patient with recurrent respiratory tract infections was cured but continued to experience relapses, and another patient with osteomyelitis improved. Two patients died (10.5%); one of them was a CF patient and died due to respiratory arrest despite eradication of the organism. The second patient who died was a newborn girl who developed necrotising enterocolitis. Finally, a diabetic patient submitted to renal transplantation was considered a treatment failure, as the acute pyelonephritis he developed was not effectively treated and led to left native kidney and graft nephrectomy.

Nine (15.8%) of 57 cases were treated with chloramphenicol, either as monotherapy in 4 cases (44.4%) [37,64,69,72] or as part of combination therapy with sulfisoxazole in 3 cases (33.3%) [4], sulfadiazine in 1 case (11.1%) [69] and tetracycline/kanamycin/nalidixic acid in the last case (11.1%) [66]. Six (66.7%) of them were cured and clinical improvement was noted in two (22.2%), one of whom died of a reason irrelevant to the infection. Finally, a 44-month-old boy with CGD (11.1%) died due to severe necrotising bilateral pneumonia. It should be noted that all these cases were reported before 1977.

Meropenem was administered in 7 (12.3%) of the 57 presented patients, 4 of whom suffered from CF [42,50,60,74]. In three (42.9%) of the courses meropenem was administered as monotherapy [12,59], whilst in the remaining four cases it was combined with either minocycline [50], tobramycin [74], clinafloxacin/rifampicin/tobramycin [60] or ceftazidime/colistin [42]. One patient (14.3%) was considered to have improved and 5 patients (71.4%) were considered to have been cured. One patient (14.3%) with CF died due to acute illness, whilst the remaining three CF patients were cured.

Seven (12.3%) of 57 cases were treated with penicillins. Four patients received piperacillin, three of them as monotherapy [35,46,62] and the remaining case in combination with gentamicin [38]. All of the piperacillin recipients had a favourable outcome. Amoxicillin/clavulanic acid [45], ampicillin [37] and carbenicillin [63] were administered in one case each. Six (85.7%) of these patients were considered as cured, whilst one (14.3%) was reported as improved.

Six (10.5%) of 57 patients received quinolone-based regimens, of whom four received ciprofloxacin either alone [43] or combined with cefoperazone [76], vancomycin/tobramycin [68] and intravitreal ceftazidime [61] in each case. Of the remaining two patients, the first was treated with levofloxacin combined with cefoperazone/sulbactam [40] and the second with a non-specified

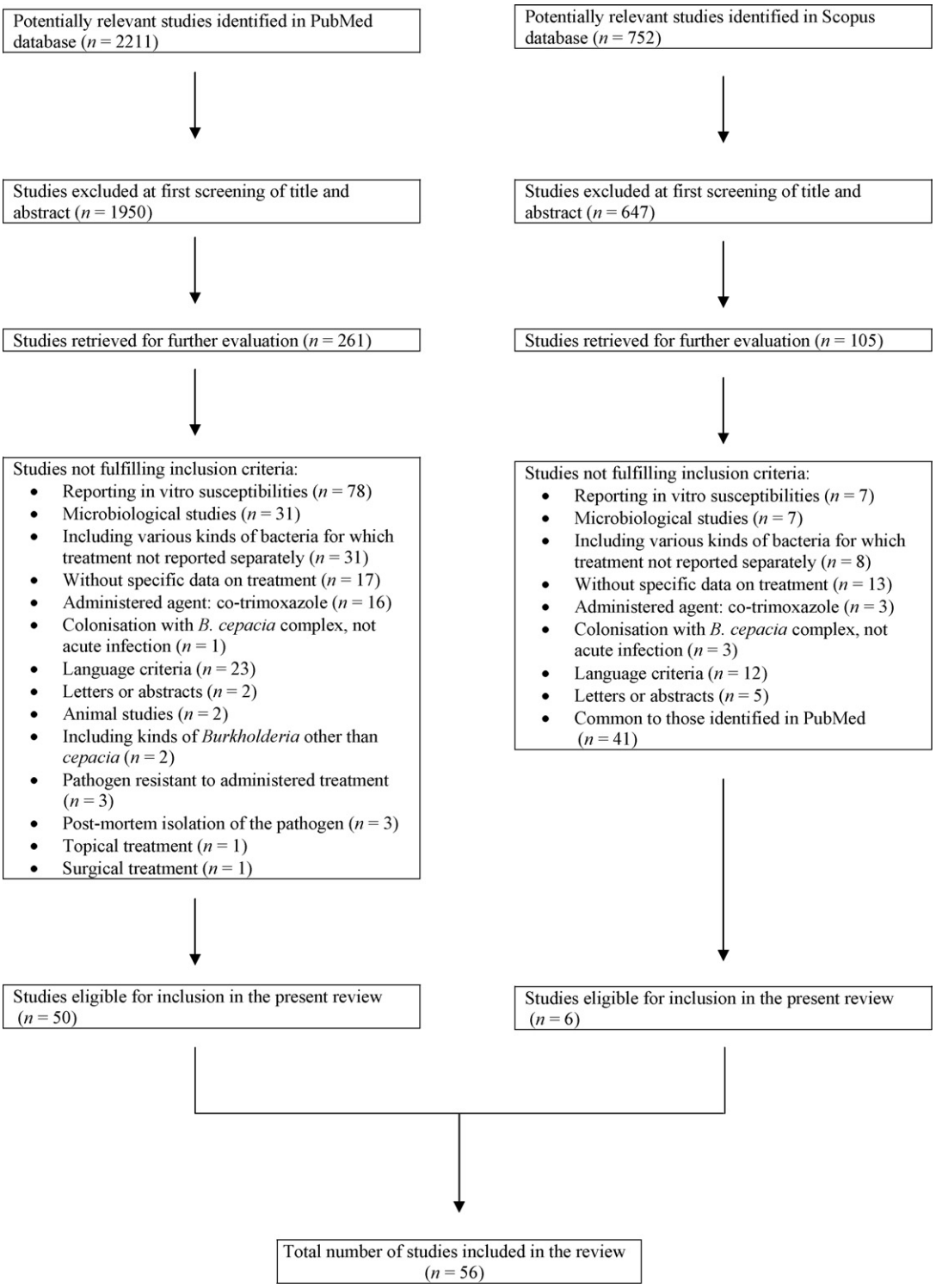

Fig. 1. Flow diagram of the selection process of the studies included in the review.

quinolone [71]. Among them, three (50%) were reported as cured, two (33.3%) were considered as treatment failures and one (16.7%) died.

Cephalosporins other than ceftazidime were administered in six cases (10.5%); two patients received ceftriaxone [58,65], two received cefepime [41,55], one cefalothin combined with kanamycin [37] and one cefotetan with imipenem/tobramycin [39]. Four (66.7%) of these six patients were cured. Two patients (33.3%) died, one due to renal failure despite eradication of the pathogen.

Of the remaining three cases, two were treated with aminoglycosides (one with amikacin [75] and the other with gentamicin [49]), whilst the third received sulfisoxazole/trimethoprim and polymyxin B [54]. All three patients (100%) were cured.

5.2. Studies other than case reports

The main characteristics of the eight retrieved studies are described in Table 2. Three retrospective studies [77–79], two

Table 1
Clinical characteristics and outcome of case reports on *Burkholderia cepacia* complex (BCC) infections.

Reference	Year	Sex/age (years)	Comments	Type of infection	Treatment	Outcome
Brescia et al. [36]	2008	F/54	Sinonasal polyposis submitted to endoscopic surgery	Sinonasal infection accompanied by mucosa hypertrophy	(1) Trimetho-prim/sulfamethoxazole; (2) oral levofloxacin; (3) ceftazidime. Endoscopic surgery	Cure
Duan et al. [40]	2007	M/78	Biventricular pacemaker	Pacemaker generator pocket infection	Levofloxacin and cefoperazone/sulbactam	Cure
Eser et al. [11]	2006	NR/63	Diabetic patient submitted to intraocular lens implantation	Post-operative endophthalmitis	i.v. ceftazidime and vancomycin, intravitreal vancomycin and ceftazidime, topical tobramycin and cefazolin	Cure
George et al. [42]	2006	M/40	CF. Colonisation with MDR *B. cepacia*	Suppurative mediastinitis; 'cepacia' syndrome	(1) i.v. meropenem and ceftazidime; (2) Meropenem, ceftazidime and colistin. Surgical drainage	Transfer to ICU. Death due to acute illness
Held et al. [44]	2006	M/5	Factor VIII deficiency (haemophilia A)	Sepsis associated with CVC	i.v. ceftazidime. Catheter removal	Cure
Marioni et al. [55]	2006	F/27	(1) Previously healthy patient; (2) cultures also revealed *Peptostreptococcus* spp. (treated with clindamycin)	Cervical necrotising fasciitis	i.v. cefepime	Cure
Miki et al. [58]	2006	M/65	T-cell lymphoma. Allogeneic stem cell transplant complicated by GvHD	Septic arthritis and bacteraemia	Ceftriaxone. Drainage and surgical management	Death due to persistent bacteraemia and multisystem organ failure (according to autopsy)
Yilmaz et al. [12]	2006	M/70	Extracapsular cataract extraction	Post-operative endophthalmitis	i.v. meropenem	Cure of the infection. Development of retinal detachment and subsequently light perception vision
Fadini et al. [41]	2005	M/77	(1) Diabetic patient; (2) cultures also revealed *Staphylococcus aureus*	Cervicomediastinal abscess	Cefepime, metronidazole, teicoplanin. Hyperbaric oxygen	Cure
Gerrits et al. [43]	2005	F/9	Previously healthy patient	Septic arthritis and community-acquired bacteraemia	(1) i.v. cefuroxime; (2) i.v. ciprofloxacin switched to oral	Cure
Hsu et al. [45]	2005	M/52	Previously healthy patient	Acute omphalitis with urachal abscess	i.v. amoxicillin/clavulanic acid	Cure
Lukela et al. [53]	2005	M/18	Previously healthy patient	Recurring pneumonia	(1) Ceftriaxone and azithromycin; (2) cefepime, clindamycin and azithromycin; (3) i.v. ceftazidime and levofloxacin	Cure
Pathengay et al. [61]	2005	M/53	Diabetic patient submitted to cataract surgery	Left eye acute post-operative endophthalmitis – recurrent endophthalmitis	Oral ciprofloxacin and intravitreal ceftazidime	No perception of light and phthisical eye after 2 months
Whitehouse et al. [73]	2005	F/40	Non-smoker with chronic sinusitis, mild asthma and epilepsy	Recurring respiratory infections	i.v. ceftazidime and tobramycin	Cure, but relapses continued
Kuti et al. [50]	2004	M/31	CF. Colonisation with MDR BCC	CF exacerbation – pneumonia	i.v. meropenem and oral minocycline	Cure (namely return to baseline state of health and patient's regular work schedule)
Mukhopadhyay et al. [59]	2004	M/56 M/53	COPD Hepatitis C and related cirrhosis (portal hypertension, oesophageal varices and ascites)	Liver abscesses Peritonitis	i.v. meropenem i.v. meropenem	Cure Improvement

Table 1
Table 1 (*Continued*)

Reference	Year	Sex/age (years)	Comments	Type of infection	Treatment	Outcome
Petrucca et al. [62]	2004	F/68	Smoldering myeloma and chronic hepatitis C	Vaginal infection	i.v. piperacillin/tazobactam	Cure
Li et al. [52]	2003	M/48	End-stage renal failure due to diabetic nephropathy; renal transplantation	Acute pyelonephritis with abscesses	Ceftazidime and piperacillin	Left native kidney and graft nephrectomy
Trujillo et al. [70]	2003	F/33	Common variable immunodeficiency	Pneumonia	Ceftazidime	Cure
Wilson et al. [74]	2003	M/20	(1) CF; previously colonised with *B. cepacia*; (2) cultures also revealed MRSA (for which he received vancomycin)	Acute pulmonary exacerbation	Desensitisation to meropenem. i.v. meropenem and tobramycin	Cure
Hung et al. [46]	2001	M/7	CGD	Neck lymphadenitis and abscess	Piperacillin. Surgical drainage and debridement	Cure
Teng et al. [68]	2001	M/69	Acute myeloid leukaemia	Bacteraemia	Ciprofloxacin, vancomycin, tobramycin	Death caused by septic shock and respiratory failure
Al Attia et al. [13]	2000	M/52	Diabetic patient	Skull osteomyelitis and multiple brain abscesses	Ceftazidime and piperacillin	Improvement
Yu et al. [75]	2000	F/40	Patient transferred to ICU because of sepsis after cosmetic surgery	Septic shock	Metronidazole and amikacin	Cure
Lau et al. [51]	1999	M/49	Valvular heart disease	Cardiac cirrhosis with cellulitis	Ceftazidime	Cure of cellulitis
Waterer et al. [71]	1999	M/32	Immunocompetent man	CAP	Quinolone	Cure
Balfour-Lynn et al. [14]	1997	F/16	CF and bilateral lung transplant	Subdural empyema	i.v. ceftazidime, chloramphenicol, vancomycin and metronidazole. Craniotomy and drainage of empyema	Cure (no neurological sequelae)
Jeffries et al. [47]	1997	F/0	Surgery for sacrococcygeal teratoma complicated by bilateral hydronephrosis and urinary ascites. Prolonged bladder catheter (Foley) drainage and irrigation	UTI	Ceftazidime	Cure
Hobson et al. [15]	1995	M/35	Chronic suppurative otitis media	Brain abscesses accompanied by infection of the left petrous temporal bone and communication between the petrous temporal bone, posterior fossa and temporal fossa	i.v. ceftazidime and ciprofloxacin. Surgical evacuation of the abscesses and left subtotal petrosectomy and cavity obliteration with cholesteatoma removal	Cure
Kahyaoglu et al. [48]	1995	F/0	Premature newborn twin girl	Sepsis	i.v. ceftazidime and imipenem	Death after development of abdominal abscess, ileocutaneous fistula and necrotising enterocolitis
		F/0	Premature newborn girl	Sepsis	i.v. ceftazidime	Cure
Dettelbach et al. [39]	1994	F/28	CF, bilateral lung transplantation, DM and a history of otitis media and recurrent sinus infections	Malignant external otitis and osteomyelitis of the temporal bone	(1) i.v. ceftazidime; (2) ceftazidime, ticarcillin/clavulanic acid, imipenem, aztreonam; (3) cefotetan, imipenem, tobramycin. Hyperbaric oxygen and surgical cleaning (mastoidectomy and endoscopic sinus surgery)	Cure
Noyes et al. [60]	1994	M/18	Double-lung transplantation for end-stage CF. Patient previously colonised with *B. cepacia*	Pleural empyema with communication to the chest wall	(1) Meropenem; (2) meropenem, clinafloxacin, rifampicin and aerosolised tobramycin. Drainage of the empyema	Cure

Saha et al. [65]	1994	M/7	Previously healthy but undernourished	Sepsis	i.v. ceftriaxone	Eradication of the pathogen. Death due to renal failure
Berry and Asmar [35]	1991	M/15	Sickle cell haemoglobin C disease	Bacteraemia	(1) i.v. ceftazidime and gentamicin; (2) i.v. piperacillin	Cure
		M/11 months	Sickle cell haemoglobin C disease	Bacteraemia	(1) i.v. cefuroxime; (2) i.v. ceftazidime	Cure
		F/23 months	Sickle cell anaemia	Bacteraemia	(1) i.v. cefuroxime; (2) i.v. ceftazidime	Cure
Koppel et al. [76]	1990	M/50	Heroin addict who sustained beating 3 weeks before admission	Intramedullary spinal cord (cervical) abscess. Development of tetraplegia	i.v. ciprofloxacin and cefoperazone. Neurosurgical drainage	Development of osteomyelitis of the C6 vertebral body
Matteson and McCune [57]	1990	F/72	Osteoarthritis. Intra-articular corticosteroid injection in the right knee 1 week before appearance of symptoms	Moderately severe septic arthritis (with joint space narrowing and osteophyte formation)	(1) Trimetho-prim/sulfamethoxazole that provoked drug rash and renewed fever; (2) i.v. chloramphenicol; (3) i.v. ceftazidime. Drainage and synovectomy	Cure
Simmonds et al. [67]	1990	M/17	CF. Patient colonised with *Pseudomonas aeruginosa*	Acute respiratory exacerbation	i.v. ceftazidime, aztreonam and lincomycin	Eradication of *B. cepacia* from sputum. Death due to respiratory arrest
Del Piero et al. [38]	1985	M/72	Glaucoma, chronic pseudophakic iritis, trabeculectomy and extracapsular cataract extraction	Acute endophthalmitis	i.v. piperacillin and gentamicin, subconjunctival piperacillin and intravitreal cefotaxime	Improvement
Marone et al. [56][a]	1985	F/45	Hydrocephalus shunt	Meningitis	i.v. ceftazidime	Cure
Kothari et al. [49]	1977	F/58	Previously healthy woman	Septic arthritis of the ankle	Gentamicin: five i.m. injections changed to i.v.	Cure
Mandell et al. [54]	1977	M/32	Heroin addiction	Endocarditis and ecthyma gangrenosum	(1) Clindamycin, kanamycin and chloramphenicol; (2) i.v. polymyxin B and oral sulfisoxazole/trimethoprim. Surgical removal of the tricuspid valve	Cure
Poe et al. [64]	1977	F/69	DM, arteriosclerotic and hypertensive cardiovascular disease and vertebrobasilar artery insufficiency	Lung abscess	Chloramphenicol. Drainage of the abscess	Clinical improvement. Death due to an apparent cerebrovascular accident (post-mortem examination not allowed)
Sieber and Fulginiti [66]	1976	M/6.5	CGD and selective IgA deficiency	Right-sided pneumonia	Chloramphenicol, tetracycline, kanamycin and nalidixic acid	Improvement
Bottone et al. [4]	1975	M/44 months	CGD	Bilateral pneumonia with a right pleural effusion	i.v. sulfisoxazole and chloramphenicol	Death due to frequent relapses leading to severe necrotising bilateral pneumonia
		M/6	CGD	Left cervical adenitis (hyperplasia with multiple abscesses and granulomas revealed on histological examination)	i.v. chloramphenicol followed by oral chloramphenicol and sulfisoxazole	Cure
		M/8	CGD	Severe pneumonia and multiple purulent skin abscesses	Chloramphenicol and sulfisoxazole	Cure
Cabrera and Drake [37]	1975	M/58	Acute anterior heart injury	Left basilar pneumonia	(1) i.v. cefalothin and i.m. kanamycin; (2) chloramphenicol	Cure
		M/66	Previously healthy man	Fever	i.v. cefalothin and i.m. kanamycin	Cure
		F/72	DM and MI	Fever	i.v. ampicillin	Cure

Table 1 (*Continued*)

Reference	Year	Sex/age (years)	Comments	Type of infection	Treatment	Outcome
Thong and Tay [69]	1975	M/30 months	Features of partially treated meningitis	Septicaemia	i.v. chloramphenicol and sulfadiazine	Cure
		F/24 months	Surgery for Hirschsprung's disease	Septicaemia	i.m. chloramphenicol	Cure
Weinstein et al. [72]	1973	M/10	Cardiac surgery for tetralogy of Fallot	Pneumonia	i.v. chloramphenicol	Cure
Phillips et al. [63]	1971	F/48	Patient in ICU with aortic and mitral valve prostheses receiving prophylactic ampicillin and methicillin	Septicaemia	i.v. carbenicillin	Cure

i.v., intravenous; NR, not reported; CF, cystic fibrosis; MDR, multidrug-resistant; ICU, Intensive Care Unit; GvHD, graft-versus-host disease; COPD, chronic obstructive pulmonary disease; MRSA, methicillin-resistant *Staphylococcus aureus*; CGD, chronic granulomatous disease; CAP, community-acquired pneumonia; UTI, urinary tract infection; DM, diabetes mellitus; i.m., intramuscular; MI, myocardial infarction; BCC, *Burkholderia cepacia* complex.

[a] Case retrieved from a case series.

prospective clinical trials [80,81], two case series [82,83] and one randomised, placebo-controlled, single-blind trial [84] were included. The outcomes are reported per patient in three studies [79,81,84] and per treatment course in four studies [78,80,82,83], whilst one study reports outcomes for both [77]. Five of them included patients with CF [80–84].

A total of 38 ceftazidime-based courses were reported in three studies [78–80], of which ceftazidime was administered alone in 17 (44.7%) and combined with another antimicrobial agent in 21 (55.3%). The combinations included: aminoglycosides in 14/21 (66.7%) (of which tobramycin was in 9/21 (42.9%)), piperacillin in 4/21 (19%), aztreonam in 2/21 (9.5%) and co-trimoxazole in 1/21 (4.8%). Twenty-six (68.4%) of 38 treatment courses resulted in a favourable outcome, and 12 (31.6%) resulted in failure, in which in 6 courses (15.8%) the patients died. In an additional study [84], ceftazidime was administered to 16 patients as monotherapy, all of whom improved (100%).

Nine ciprofloxacin-based courses were administered, of which eight courses were as monotherapy [78,79] and one combined with aztreonam [79]; seven (77.8%) of nine courses resulted in a favourable outcome and two courses (22.2%) failed and the patients died. In a study [81] that included 30 patients from whom 15 BCC isolates were cultured, all of the patients who received ciprofloxacin monotherapy improved (100%).

Fifteen carbapenem-based courses were administered, nine (60%) of which included meropenem [82] and the remaining six imipenem [78]. Five (83.3%) of six imipenem courses had a favourable outcome and one (16.7%) failed and the patient died. Six (66.7%) of nine meropenem courses had a favourable outcome, whilst in 3 (33.3%) the condition of the patient remained stable. No deaths were reported.

Five patients received 12 treatment courses of temocillin [83]. Nine (75%) of 12 courses were reported as clinical improvement, one (8.3%) as partial response to treatment and one (8.3%) as failure. One patient (8.3%) died due to respiratory failure.

Finally, nine patients were treated with tobramycin [77], eight of which were as monotherapy and one in combination with cefoxitin. Eight (88.9%) of nine patients needed to be hospitalised to receive further treatment, whilst two patients (22.2%) died (one in hospital).

6. Evaluation of the available clinical evidence

The main finding of our review regarding the management of BCC infections when the administration of co-trimoxazole is inappropriate or ineffective is that there are alternative antimicrobial treatments to be used. These consist of ceftazidime, meropenem and penicillins, mainly piperacillin, either as monotherapy or in combination with other antibiotics.

BCC consists of difficult-to-treat pathogens that exhibit both intrinsic and acquired resistance to many commonly used antibiotics. Among the intrinsic resistance mechanisms, innate decreased permeability of the bacterial membrane is believed to be responsible for resistance to aminoglycosides, polymyxins, β-lactams [31,85,86] and chloramphenicol [87]. Efflux pumps have also been considered as a mechanism of intrinsic resistance, mainly for chloramphenicol, trimethoprim and fluoroquinolones [88–90]. Production of β-lactamases confers resistance to β-lactams [91], whilst a substantial outer membrane hydrophilic permeability barrier protects the bacillus from all hydrophilic antimicrobial agents [92]. Other mechanisms reported in the literature include production of modifying enzymes other than β-lactamases and alteration of antibiotic targets [91,93].

Table 2
Characteristics of retrieved cohorts and trials on *Burkholderia cepacia* complex (BCC) infections in published relevant cohorts and trials.

Reference	Year	Study design	Comments	Type of infection	No. of patients	No. of isolates	Antibiotic	No. of treatment courses	Outcome
Huang et al. [78]	2001	Retrospective cohort	40 hospitalised cases, 2 community-acquired endocarditis cases	Bacteraemia	40	42	Ceftazidime	13	2 deaths
							Ceftazidime and aminoglycoside	5	0 deaths
							Ciprofloxacin	6	2 deaths
							Imipenem	6	1 death
Ciofu et al. [82]	1996	Case series	Patients with CF	Chronic bronchopulmonary infection	5	5	Meropenem	10 (1 interrupted due to drug fever)	6/9, improvement; 3/9, stable
Keizur et al. [79]	1993	Retrospective	Patients submitted to transrectal ultrasound-guided needle biopsy of the prostate	Acute UTI (prostatitis)	6	6	Oral ciprofloxacin	2	All patients responded to therapy
							Aztreonam and ceftazidime	2	
							Aztreonam and ciprofloxacin	1	
							Aztreonam and vancomycin	1	
Taylor et al. [83]	1992	Case series	Patients with CF. Every patient was also infected with *Pseudomonas aeruginosa*	Acute respiratory exacerbation	5	12	Temocillin	12	9/12, clinical improvement; 1/12, partial response; 1/12, failure; 1/12, death due to respiratory failure
Gold et al. [84]	1987	Placebo-controlled single-blind randomised trial	Patients with CF. Two patients had *B. cepacia*. Most patients had both *B. cepacia* and *P. aeruginosa*	Acute respiratory exacerbation	16	12	Ceftazidime	NA	16/16, clinical improvement
Goldfarb et al. [81]	1987	Prospective clinical trial	Patients with CF	Acute respiratory exacerbation	30 (not all had *B. cepacia*)	15	Ciprofloxacin	NA	All patients clinically improved
Gold et al. [80]	1983	Prospective clinical trial	Patients with CF colonised with *B. cepacia*	Acute respiratory exacerbation	14	NA	Ceftazidime	4	6/18, improvement; 8/18, failure; 4/18, death
							Ceftazidime and tobramycin	9	
							Ceftazidime and piperacillin	4	
							Ceftazidime and SMX/TMP	1	
Berkelman et al. [77]	1982	Retrospective	Outpatients under chronic dialysis therapy for end-stage renal failure	Peritonitis and sepsis	1	NA	Tobramycin and cefoxitin	1	Death
				Peritonitis	8	NA	Tobramycin	8	8 patients needed hospitalisation, 1 death

CF, cystic fibrosis; UTI, urinary tract infection; NA, not available; SMX/TMP, sulfamethoxazole/trimethoprim.

Apart from intrinsic mechanisms, acquired resistance has also been observed against commonly used antibiotics for infections caused by BCC and other common pathogens in CF patients. It has been ascribed mainly to the emergence of hypermutable bacteria [21,94]. Acquired resistance may be realised during therapy or through induction of cross-resistance among different classes of antibiotics [87,95].

The types of infections that can be caused by BCC range widely. In patients with CF, BCC infection can result in asymptomatic carriage, chronic infection or 'cepacia syndrome'. The latter is a form of progressive necrotising pneumonia, accompanied by an acute systemic infection such as bacteraemia, and leads to death from septicaemia or respiratory failure [1,29,96]. The mortality rate in chronically infected individuals is 20–35% [29].

In ambulatory patients, BCC causes endophthalmitis following eye surgery [11,12], community-acquired pneumonia [53,71] and community-acquired bacteraemia [43]. In heroin addicts it has been reported to cause endocarditis [54], whilst pneumonia is frequent in CGD [4,66]. It is also common in immunocompromised patients suffering from malignancies [58,62,68], haemoglobinopathies [35] and other types of immunodeficiency [41,52,70].

In hospitalised patients, BCC is increasingly recognised as a pathogen of pneumonia, urinary tract infections and bacteraemia [1,79,97–99]. This is attributed to the fact that it can contaminate anaesthetics, disinfectants and antiseptics such as chlorhexidine and povidone-iodine, ventilator nebulisers, saline solution and catheters [100–107]. Catheters, especially when they are implanted for long periods of time, can facilitate bacterial colonisation and biofilm formation [108]; their removal in such cases is of great value [102].

The suggested treatment options for BCC infection are generally limited. Huang et al. [78] report susceptibility rates of *B. cepacia* to imipenem, quinolones, trimethoprim/sulfamethoxazole and third-generation cephalosporins, mostly ceftazidime, ranging from 64% to 95%. In combination with clinical data, ceftazidime and co-trimoxazole are suggested as drugs of choice. Lu et al. [102] report susceptibility rates to ceftazidime, piperacillin, minocycline and cefotaxime higher than 80%. As combination therapy did not have lower mortality rates, it was not considered necessary and the authors suggested ceftazidime or piperacillin as the preferable empirical treatment. A more recent study suggests administration of meropenem in combination with at least one of the following: minocycline, amikacin or ceftazidime [109].

The main limitation of our review is the fact that co-trimoxazole was considered the treatment of choice for BCC. This is mainly based on early reports from patients with CF. Although there are alternatives since the advent of new antibiotics, no studies were conducted to compare other potent antimicrobial agents against this group of pathogens. Furthermore, data are provided mainly from case reports and case series. Conclusions drawn from these types of studies are not likely to influence clinical decision-making greatly owing to the low quality of data provided. In addition, owing to the absence of specific guidelines for the treatment of BCC infections, a variety of antimicrobial agents have been administered to patients presented in the included studies.

Furthermore, there has been a subsequent heterogeneity in the outcomes reported, as certain articles defined infection course as the primary outcome, whilst others the mortality rates. It should be noted that there might be a publication bias regarding the effectiveness of the included therapeutic regimens, as case reports presenting negative outcomes of those regimens would probably be less likely to be published. It should be emphasised that there are some pathogens of the BCC that have a better outcome or are even spontaneously cured, such as *B. multivorans*. However, this is not the rule and BCC infections should be treated.

It is interesting that it is not clear whether combination therapy is more effective than monotherapy for the treatment of BCC infections [110]. The findings of this review do not shed light on the question and this point remains to be examined further.

7. Conclusion

BCC has been identified as an important group of pathogens of patients suffering from CF, hospitalised patients and, rarely, of ambulatory patients. The management of BCC infections is generally difficult because of the high levels of resistance, inherent and acquired, to many classes of antibiotics. Despite the various limitations in the synthesis of the available relevant evidence (acknowledged above), the data included in this review suggest that ceftazidime, meropenem and penicillins, mainly piperacillin, either alone or in combination with other antimicrobial agents, could be considered as alternative therapeutic options for BCC infections, beyond co-trimoxazole. The susceptibility patterns in each case should be examined in order to specify the most appropriate treatment. However, clinical data are not sufficient and further clinical experience is required to clarify the appropriateness of antibiotics used for the treatment of patients with BCC infections.

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