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Review Article

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In-vivo and In-vitro Therapeutic Perspectives in The Treatment of *Burkholderia cepacia* Complex Infections: A Review

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Abstract: *Burkholderia cepacia* complex (Bcc) is an opportunistic, widespread pathogen. It first came out as a deadly lung infection with a high rate of morbidity and death among cystic fibrosis (CF) individuals. It is not only harmful to CF patients but is also thought to be a significant pathogen in other susceptible individuals. It has recently spread beyond the limits of CF and identified as a cause of healthcare-associated infections. Treatment of Bcc infections is considered a complex problem. It is a multi-drug-resistant microorganism that has different innate and acquired resistance mechanisms. Evaluating information retrieved from *in-vitro* and *in-vivo* studies was necessary to direct antibiotic therapy for infected patients. A review was conducted by searching the electronic database PubMed using MeSH terms in the search query aiming to retrieve more relevant results over the last ten years from 2015 to 2024. Data describing clinical diagnosis, different treatment regimens with durations, outcomes after treatment, and the antimicrobial susceptibilities were extracted from the *in-vitro* antimicrobial susceptibility investigations as well as *in-vivo* studies and then analyzed to address various aspects including the promising *in-vivo* therapy of Bcc infection in CF and non-CF patients, consistency between *in-vivo* studies and *in-vitro* susceptibility studies, and treatment duration. A total of 56 different studies were found eligible to be included in our review. Treatment mostly depended on combination therapy having ceftazidime either alone or combined with avibactam and meropenem as the most frequently used intravenous antibiotics while cotrimoxazole and fluoroquinolones were the most frequently used oral antibiotics.

Keywords: *Burkholderia cepacia*; cystic fibrosis; non-CF; in-vivo; in-vitro; antibiotic; susceptibility; combination

1. INTRODUCTION

Bacteria belonging to the genus *Burkholderia* were first identified in the 1950s. They are Gram-negative bacteria that can be found in nature, frequently in soil, the rhizosphere of plants, or water. Some species in this genus can infect people, plants, and animals, while other species have positive impacts that are significant for agriculture or industry[1]. Walter Burkholder identified it as a pathogenic bacterium in plants that caused onion rot in the middle of 1940s. It was at first known as *Pseudomonas cepacia*. The *Burkholderia* genus is a member of the beta-proteobacteria class with the Burkholderiales order and Burkholderiaceae family. According to a 1992 proposal, seven species were separated from *Pseudomonas* ribosomal RNA group II based on DNA–DNA homology, sequences of 16s rRNA, and composition of cell-membrane lipid[2]. There are currently about 100 species of *Burkholderia*[3]. Within the *Burkholderia* genus, *Burkholderia cepacia* complex (Bcc) is a subgroup[4].

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It is an oxidase-positive, catalase-positive, aerobic, non-spore-forming, non-sugar-fermenter bacteria. It contains species that are genetically different but have similar phenotypes[5,6]. Currently, Bcc has approximately 21 species that were known previously as genomovars (species that are closely related)[7]. These bacteria typically contain three chromosomes in addition to large plasmid in their genomes, which range in size from 7 to more than 9 million base pairs (Mbps)[8]. Bcc genomes are assumed to be more flexible to lose and gain genes due to their massive size. This extensive genetic capacity increases Bcc adaptability in infections and biological processes[6].

Bcc can survive in liquid media even with poor nutrients, colonization of this pathogen in the hospital setting has led to serious outbreaks. Different sources of infection have been reported as contaminated albuterol solution for nebulization[9], injection fluids[10], intravenous and liquid medication[11], chemical detergents[12], and contaminated mouthwash[13]. Bcc is linked to three main human infection categories that are significant to respiratory and intensive care patients. The first is healthcare-associated bacteremia, which usually develops in intensive care units and is thought to be transmitted through instruments like bronchoscopes and central venous catheters[14]. The second, for which Bcc is most known, is the respiratory tract infection in CF patients.

Burkholderia cenocepacia has been recognized as the most virulent species that was related to cepacia syndrome, a fatal consequence associated with extremely high mortality due to overwhelming pneumonia and bacteremia, although *B. multivorance* was noted as the species most frequently encountered in the CF community[15]. Another serious consequence of *B. cenocepacia* infection besides the disease severity is that it drastically limits the number of CF patients who are capable of receiving lung transplants due to the high risk of postoperative sepsis and death[16]. The other particularly susceptible hosts are the individuals with chronic granulomatous medical conditions whose neutrophils have defects in oxidative clearance of phagocytosed microorganisms[17]. The third type of Bcc infection which is considered the rarest one is community-acquired pneumonia in individuals who are immunocompetent with no suspected or documented CF illness[18].

Bcc infections are challenging to treat. Cotrimoxazole and ceftazidime can be considered first-line treatment[19] but *in-vitro* susceptibility testing results revealed that resistance of Bcc isolates ranged between 10 to 40% against cotrimoxazole and 30 to 40% against ceftazidime[20]. In addition to decreased susceptibilities to these first-line antibiotics, drug intolerance, especially to cotrimoxazole, may also restrict choices of therapy[21].

The microorganism's resistance to several existing antimicrobial agents in addition to the shortage of more recent and potent agents are the two major challenges in the management of Bcc-infected patients. Species of Bcc were reported to have high levels of inherent resistance to a wide range of antimicrobial agents, such as cephalosporins (first and second generations), penicillin, aminoglycosides, polymyxins, and fosfomycin. A fact that makes these infections are extremely difficult to treat which in some cases could be fatal[22].

The goal of this review is to analyze the available information regarding treatment of different Bcc infections, in addition to *in-vitro* susceptibility testing studies in order to identify the possible therapeutic options and potential areas for additional study.

2. METHODS

2.1. Search strategy

The electronic database PubMed was searched using search MeSH terms for '*Burkholderia cepacia* complex' AND 'drug effect' as the selected subheading in the PubMed search builder options for articles published from 2015 till 2024. Advanced search including the term 'antimicrobial' to the previous search builder was performed. Titles and abstracts were screened and the full text of potentially eligible studies was retrieved then the whole article was evaluated for eligibility.

2.2. Inclusion criteria

For the current review, we included clinical studies of CF and non-CF patients with Bcc infection. The included studies were required to provide information regarding antimicrobials used for the Bcc infection(s) even if treatment was not the main goal of the investigation. These studies might include case reports, case series, controlled clinical trials, or observational. We also incorporated studies

that involved antimicrobial susceptibility testing against Bcc clinical isolates.

2.3. Aspects that the review discussed

The different aspects that this review discussed were the promising *in-vivo* therapy of Bcc infection in CF patients, promising *in-vivo* therapy of Bcc infection in non-CF patients, consistency between *in-vivo* studies and *in-vitro* antimicrobial susceptibility studies, and the duration of treatment.

2.4. Extracted data

There were two different types of data extracted from the eligible studies, one included *in-vitro* studies while the other included *in-vivo* studies. In the first, the study's publication year, collection period, clinical diagnosis of the different cases which were the source of the clinical isolates, sample size, antimicrobial susceptibility, and publication region/country were all retrieved (Table1) while the second type of data included publication year, study design, sample size, clinical diagnosis, antimicrobial susceptibility results, different treatment regimens, treatment duration and the treatment outcome in addition to region/country from where the study was reported (Table 2).

3. RESULTS and DISCUSSION

3.1. Search results

A total of 203 studies resulted from the search using the MeSH terms option on PubMed. Based on the inclusion criteria, 89 studies were initially seen to be eligible for inclusion and after screening the content 33 studies were excluded, 7 were review articles, 7 were correspondence/editorial letters, and 19 were discussing experimental novel antimicrobial compounds. Finally, 56 studies were included in this review as they were considered eligible: 28 were *in-vivo* studies in addition to 28 *in-vitro* studies. A flow chart of the research results is summarized in figure.

3.2. Promising *in-vivo* therapy of Bcc infection in CF patients

CF patients experience recurrent infections, and as they get older, different microorganisms have been found in their respiratory tracts[76]. Bcc is believed to be responsible for serious respiratory tract infections within CF populations. Compared to infections with other infectious agents like *Pseudomonas aeruginosa*, the Bcc infections reported in the early reports were much more virulent, and the consequence was an uncontrollably rapid clinical deterioration that killed nearly 10% of patients (a clinical manifestation known as cepacia syndrome)[77]. Beyond the growing severity of the disease, a major effect of Bcc infection is that it significantly reduces the proportion of CF patients eligible for lung transplants because of the increased risk of postoperative sepsis and death[78]. According to data retrieved from the included studies in our review, 9 *in-vivo* studies have focused on the treatment of Bcc infection in CF patients in the last 10 years. These studies included 5 case reports, 1 clinical trial, and 3 retrospective analyses describing a total of 40 patients.

Strategies of treatment were heterogeneous but the majority included a combination of intravenous, oral, and nebulized antibiotics. Levofloxacin, ceftazidime, meropenem, minocycline, cotrimoxazole, and chloramphenicol are among the few antibiotics that can be used to treat Bcc infections due to its broad range of inherent resistance to antibiotics[79]. Most studies reported in the last 10 years included levofloxacin, ceftazidime, meropenem, and cotrimoxazole. All included *In-vivo* studies on CF patients had a combination of 2 or more of the previously mentioned antibiotics except for the clinical trial[54] and the retrospective study that focused on the novel ceftazidime-avibactam[62]. Only one case study reported patient death because of the Bcc infection even with treatment by the combination of ceftazidime-avibactam, cotrimoxazole, and ciprofloxacin, noting that the susceptibility test for the *B. cepacia* isolated from the patient showed resistance to all beta-lactams and cotrimoxazole[63] while a retrospective study declared that 50% of treated patients could eradicate the bacterium[66]. Other studies' outcomes ranged from clinical improvement to complete eradication. Both chloramphenicol and minocycline were included in the treatment strategy in one retrospective study concerned with CF patients[62]. Chloramphenicol was previously included in the CLSI 2022 suggested antimicrobial agents for reporting and investigation against Bcc.

In developed countries, chloramphenicol was partially abandoned as systemic administration of it is linked to deadly aplastic anemia[80] and later on, it was excluded from the CLSI 2023 edition. Among the antibiotics that weren`t suggested for Bcc treatment but had been included in the treatment combinations, tobramycin (IV or inhaled), temocillin, ciprofloxacin, and inhaled aztreonam. Based on *in-vitro* susceptibility, Garcia *et al*

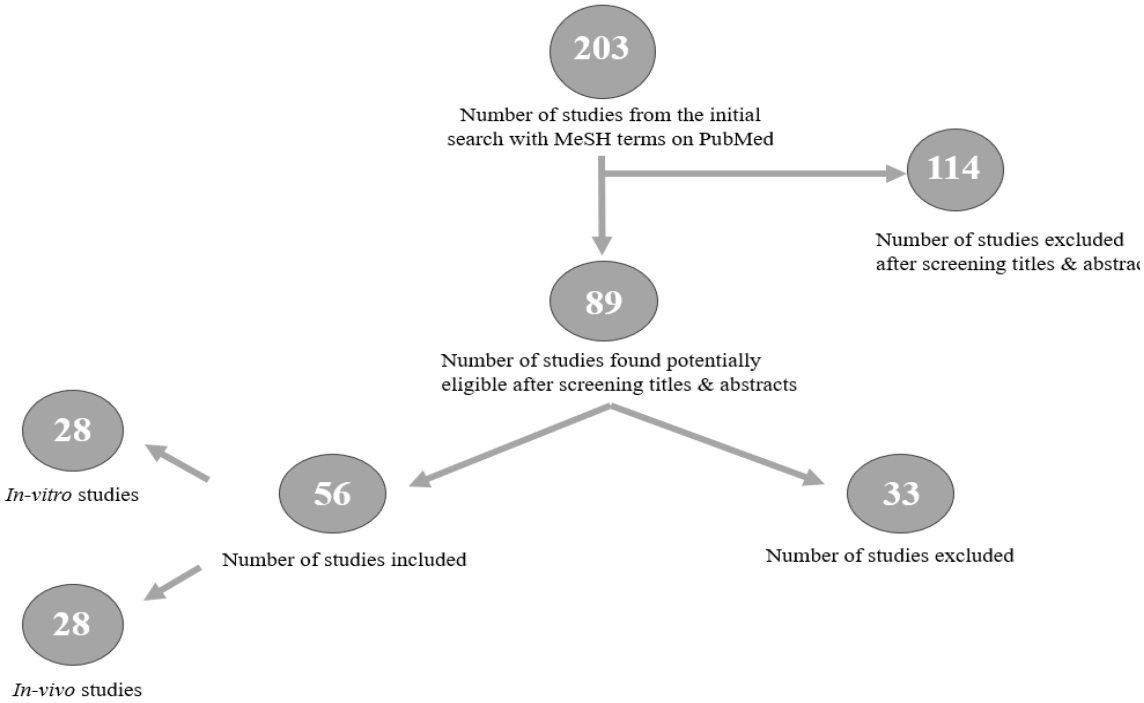

Figure 1. Flow chart of the selection process for the studies included in the review.

developed a protocol for Bcc eradication which comprised of intensive combination regimen of intravenous, inhalation, and oral antibiotic therapies. The protocol included an induction period for 21 days and the antibiotics included were intravenous tobramycin 6 mg/kg daily, intravenous ceftazidime 2 g every 8 hours, oral cotrimoxazole 800/160 mg twice daily, inhaled tobramycin 300 mg twice daily followed by a consolidation period of 2 months with oral cotrimoxazole 800/160 mg twice daily and inhaled tobramycin a 300 mg twice daily. All six participants in the retrospective study had clinical stability and their Bcc infection was cleared up[59].

A total of 7 out of the 9 included studies had nebulized antibiotics in the treatment strategy. One of them with colistimethate (due to the mixed infection with *Pseudomonas aeruginosa*) while six had inhaled aminoglycoside mostly tobramycin and one had inhaled aztreonam. Both adults and children CF patients with chronic Bcc infection were enrolled in a clinical trial to test inhalation powder of tobramycin that was delivered via Podhaler. It was administered two times per day for 28 days. The trial demonstrated that the medication can reduce the bacterial density in sputum as well as pulmonary inflammatory markers but it was unable to significantly improve lung function[54]. Inhaled antibiotic clinical trials for Bcc infection in CF patients are few. Tullis *et al* had conducted the largest, placebo-controlled, double-blind, 24-week trial in 100 CF patients having chronic infection with Bcc and treated with continuous inhaled aztreonam. It was observed that the sputum bacterial density increased by about 1.5 log (CFU/ml) after 24 weeks of treatment[81], in contrast to the latest clinical trial which observed a 1.4 log decrease in sputum bacterial density after 28 days of treatment with tobramycin inhalation powder[54].

Burkholderia species are known to exhibit resistance mechanisms that involve the generation of beta-lactamases, which include class A beta-lactamases (as PenA and PenB), class C beta-lactamases (as AmpC), as well as class D beta-lactamases. The lower susceptibility of beta-lactam antibiotics against Bcc species is also attributed to non-beta-lactamase-mediated resistance, including reduced permeability of the outer membrane and efflux pumps[82]. The recently introduced beta-lactamase inhibitor avibactam can prevent the enzymatic hydrolysis of class A, C, and some class D beta-lactamases, which in turn restores sensitivity to ceftazidime antibiotic[22].

Because ceftazidime-avibactam has a significantly better *in-vitro* susceptibility than ceftazidime alone, it offers an innovative therapeutic alternative against Bcc. Ceftazidime susceptibility increases by nearly 20% when avibactam is added[83]. In our review, 4 case studies had ceftazidime-avibactam as a part of their treatment strategy and only one study reported patient death after a treatment regimen of ceftazidime-avibactam combined with ciprofloxacin and cotrimoxazole for 3 weeks[63].

In a review conducted by Bogaart and Manuel, it was reported that the main antibiotic options for Bcc infection are cotrimoxazole, ceftazidime, and levofloxacin while alternative treatment includes minocycline and meropenem. For MDR Bcc, ceftazidime-avibactam is the main antibiotic for treatment and cefiderocol is an alternative option while for MDR Bcc resistant to ceftazidime-avibactam, the main treatment options are imipenem-relabactam and piperacillin-tazobactam + ceftazidime-avibactam while cefiderocol and temocillin are alternatives[84].

3.3. Promising *in-vivo* therapy of Bcc infection in non-CF patients

Bcc is becoming highly recognized as a serious pathogen in humans, especially in individuals with compromised immune systems and those receiving hospital care who can get the infection from contaminated objects or from other infected patients[85]. The increasing number of reports of hospital-acquired infections caused by Bcc led to its recognition as an emergent causative agent of nosocomial infections in patients who are not suffering from CF, particularly in cancer patients. There have been more incidences of Bcc-caused bacteremia among hospitalized non-CF patients[8]. In addition to being extremely virulent, five species of Bcc (*B. cepacia, B. cenocepacia, B. multivorans, B. dolosa*, and *B. contaminans*) can spread via aerosol droplets which make them capable of rapidly infecting hospitalized patients[86]. Bcc has also been isolated from otitis media infections, pediatric neck infections, and pharyngeal infections in immunocompetent individuals[8]. According to data retrieved from the included studies in our review, 17 *in-vivo* studies have focused on the treatment of Bcc infection in non-CF patients in the last 10 years. These studies included 10 case reports, 2 case series, 1 cohort study, and 4 retrospective analyses describing a total of 755 patients. Most infections caused by Bcc reported in the included studies were bloodstream infections although nosocomial pneumonia, osteomyelitis, endocarditis, keratitis, endophthalmitis, intraabdominal abscess, exit-site infection, and community-acquired pneumonia were also reported.

Similar to CF infections, treatment strategies of non-CF patients were heterogeneous but the majority included a combination of antibiotics. A total of 4 out of the 17 *in-vivo* studies depended on monotherapy treatment strategy and all were associated with improvement in the clinical condition of the patient. Out of them, 3 studies were on keratitis patients which were treated with topical antibiotics, either ceftazidime, moxifloxacin, levofloxacin, or amikacin. Two studies used ceftazidime[57] /moxifloxacin monotherapy[68] and demonstrated infection-resolving while the third demonstrated improvement in clinical condition to the treatment with levofloxacin in 9 patients, ceftazidime in 6 patients, and amikacin in 2 patients although surgical interventions were needed in some patients[70]. One study included a case report for a patient with nosocomial pneumonia after cardiac surgery who was treated with ceftazidime antibiotic and his condition improved steadily[58].

Two retrospective studies conducted on a large number of patients with bloodstream infections revealed that no antimicrobial regimen was associated with significantly better outcomes[64,69]. On the other hand, the large cohort study included non-CF patients having bloodstream infection with Bcc conducted by El Chakhtoura *et al* revealed that these infections were common in critically ill elderly patients, many of whom had central venous catheters and were associated with high mortality rates. According to their study, the best approach to enhance these patients' probability of survival is to control the infection source and start effective antibiotic treatment as soon as possible. The antibiotics with the greatest likelihood of being effective were cotrimoxazole and fluoroquinolones. Unexpectedly high ceftazidime resistance was noted , which was probably caused by beta-lactamases. Despite cotrimoxazole's extensive activity, the majority of patients received treatment with other agents, and there was no change in the mortality rate[19].

Out of the *in-vivo* included studies concerned with non-CF patients, 7 had antibiotic combination treatment regimens and were associated with good outcomes. They include a case report of recurrent osteomyelitis and bacteremia[53], refractory *B. cepacia* bacteremia from consolidation pneumonia[61], endogenous endophthalmitis[67], sepsis secondary to pneumonia[71], community-acquired pneumonia[73], perisplenic intraabdominal abscess[74], and a case series of 44 patients had bacteremia, skin and soft tissues infections, and vertebral osteomyelitis[72]. All of which had improvement in clinical condition due

Table 1. Information retrieved from *in-vitro* studies

No.	Publication year	Collection period	Clinical diagnosis	Sample size	Susceptibility (%) / MIC	Country	Ref.
1	2015	Not mentioned	CF	180 *Bcc* isolates	TOB MIC50 and BIC50 were 100 ug/ml.	Canada	(23)
2	2016	One month	Neonatal bacteremia	12 *Bcc* isolates	CAZ (100%), COT (100%), CHL (91.6%), AMK (83.3%), MRP (83.3%), TZP (83.3%), and CIP (75%).	India	(24)
3	2016	From 2008 to 2013	Healthcare-associated BSI manifested as bacteremia	53 *Bcc isolates*	ISP (8%), AMK (6%), CN (4%), and TOB (4%). All MIC90 were >128 ug/ml.	Taiwan	(25)
4	2016	From 2001 to 2013	Not mentioned	278 *Bcc isolates*	COT (52.5%), DOX (46.4%), and MIN (45.9%).	UK	(26)
5	2016	During 2013	Not mentioned	30 *Bcc* isolates	COT (100%) with MIC90, 2µg/ml, CAZ (93.1%) with MIC90, 4µg/ml, MIN (93.3%) with MIC90, 4µg/ml, and MRP (89.7%) with MIC90, 8µg/ml.	USA, Latin America, Europe, Asia-Pacific, and Mediterranean region.	(27)
6	2016	From 2004 to 2014	Bacteremia in non-CF	14 *Burkholderia cepacia* isolates	CAZ (92.8%), LVX (85.7%), MIN (85.7%), COT (85.7%), and MRP (78.5%).	Korea	(28)
7	2017	From 2013 to 2015	CF and non-CF infections	161 *Bcc* isolates	TZP (94.4%), CAZ (85.7%), MRP (83.1), COT (74.7%), MIN (73.3%), AZT (66.7%), CIP (57.5%), AMK (45.3%), and IMP (34.8%).	UK	(29)

No.	Publication year	Collection period	Clinical diagnosis	Sample size	Susceptibility (%) / MIC	Country	Ref.
8	2017	From 2005 to 2016	CF	221 *Bcc* and *Burkholderia gladioli* isolates	COT (MIC50, ≤ 1 ug/ml), LVX (MIC50, ≤ 1 ug/ml), TGC (MIC50, ≤ 2 ug/ml), CIP (MIC50, ≤ 2 ug/ml), MRP (MIC50, 2 ug/ml), MIN (MIC50, 2 ug/ml), Ceftolozane-tazobactam (MIC50, 2 ug/ml), TZP (MIC50, ≤ 4 ug/ml), DRP (MIC50, 4 ug/ml), CAZ (MIC50, 4 ug/ml), CHL (MIC50, 16 ug/ml), AZT (MIC50, 16 ug/ml), TOB (MIC50, >16 ug/ml), and AMK (MIC50, 64 ug/ml).	Canada	(30)
9	2017	From 2011 to 2014	CF	98 *Bcc* isolates	MRP (82.3%), CAZ (70.5%), COT (70.5%), MIN (52.9%), CHL (29.4%), LVX (17.6%), and TCC (5.8%).	Brazil	(31)
10	2017	Not mentioned	CF	50 *Burkholderia multivorans* isolates	CAZ-AVI (100%), CAZ (68%), COT (62%), MIN (36%). Resistance to TOB, IMP, and CIP was >90 %.	USA	(32)
11	2017	Not mentioned	CF	16 *Bcc* isolates	MOX-CAZ combination (100%) Adding colistin in low dose improved the combination effect.	Canada	(33)
12	2018	From 2011 to 2015	CF	68 *Bcc* isolates	MIN (76%), MRP (76%), CAZ (76%), and COT (54%) against *Burkholderia contaminans* isolates. CAZ (53%) and MRP (53%) against *Burkholderia cenocepacia* isolates while 100% were resistant to COT and MIN. CAZ (40%), MIN (40%), and COT (20%) against *Burkholderia seminalis* while 60% had intermediate sensitivity to MRP.	Argentina	(34)
13	2018	From 2012 to 2016	CF	91 *Bcc* isolates	COT (82%), CAZ-AVI (81%), CLZ-TAZ (63%). For TMO, CAZ, TZP, and MRP, at least 50% of isolates were sensitive. AMK, TOB, CST, CIP, and TGC had little or no activity.	Belgium	(35)
14	2018	From 2013 to 2015	Bacteremia in non-CF patients	54 *Bcc* isolates	COT (87%), MRP (87%), CAZ (77.8%), and LVX (44.4%).	Taiwan	(36)
15	2018	From 2001 to 2010	CF	39 *Burkholderia cenocepacia* isolates	*Burkholderia cenocepacia* isolates were resistant to CLZ-TAZ with median MICs >256 ug/ml	UK	(37)

No.	Publication year	Collection period	Clinical diagnosis	Sample size	Susceptibility (%) / MIC	Country	Ref.
16	2019	From 2014 to 2018	Pneumonia, BSI, UTI, intra-abdominal infections, skin infections, and others	101 *Bcc* isolates	COT (93.1%), CAZ (91.0%), MRP (89.1%), and MIN (88.1%)	USA	(38)
17	2019	Not mentioned	CF	151 isolates including *Bcc* and *Burkholderia gladioli* isolates	PIP-AVI (99.3%). The PIP-AVI is not available clinically so the combination of CAZ-AVI plus TZP was tested having 99% susceptible isolates.	USA	(39)
18	2019	From 2015 to 2016	RTI, UTI, skin and soft tissue, BSI, or intra-abdominal infections.	89 *Bcc* isolates	Cefiderocol MICs ≤4 mg/L for 94.4% of *Bcc* isolates. Five *Bcc* isolates had a cefiderocol MIC ≥8 mg/L and all were *Burkholderia multivorans.* The cefiderocol MIC90 was ≥16-fold which was lower than the MIC90 of CFPM, CAZ-AVI, CLZ-TAZ, CIP, CST, and MRP.	North American and European clinical laboratories	(40)
19	2020	From 2005 to 2011	Septicemic CF patients	44 *Bcc* isolates	TZP (95%), CAZ (89%), COT (75%), MRP (55%), TCN (25%), and LVX (14%).	India	(41)
20	2020	From 2013 to 2018	Nosocomial infections	38 *Burkholderia cepacia* isolates	LVX (76.9%), COT (58.8%), TGC (56.3%), TCC (44.4%), MRP (38.7%), TZP (38.2), AMK (28.9%), CIP (27.3%), CN (26.7%), IMP (25%), CAZ (21.6%), AMP-SUL (15%), CTX (7.5%), and CST (5.4%).	Turkey	(42)
21	2020	From 2013 to 2018	Vascular access infections in hemodialysis patients	13 *Bcc* isolates including 3 *Burkholderia contaminans* and 10 *Burkholderia cepacia*	The 3 *Burkholderia contaminans* isolates and 4 out of the 10 *Burkholdeia cepacia* isolates were CST resistant, 5 *Burkholdeia cepacia* were CN resistant, and 4 were IMP resistant.	Taiwan	(43)
22	2020	From 2007 to 2016	Different types of infections in non-CF patients	530 *Bcc* isolates	COT susceptibility was 80, 70, and 89%, CAZ was 83, 60, and 65%, and MRP was 60, 70, and 43% at the beginning, middle, and end of the study, respectively. TCN susceptibility was 43% at the beginning of the study and that to MIN was 100% mid-study and 74% at the end. LVX susceptibility decreased from 84 (in 2014) to 76% (in 2016).	India	(44)

No.	Publication year	Collection period	Clinical diagnosis	Sample size	Susceptibility (%) / MIC	Country	Ref.
23	2021	Not mentioned	Not mentioned	150 *Bcc* and *Burkholderia gladioli* isolates	CAZ-AVI (90%), IMP-REL (71.3%), CAZ (62.6%), and IMP (16%).	USA	(45)
24	2021	Not mentioned	CF	50 *Burkholderia cenocepacia* plus 50 *Burkholderia multivorans* isolates	CAZ (43%), COT (39%), TZP (23%), MIN (21%), MRP (15%), and LVX (9%). CHL and CIP (1%).	USA	(46)
25	2021	From 2014 to 2019	Not mentioned	226 *Bcc* isolates	COT (89.8%), MRP (88.9%), CAZ (87.1%), and MIN (86.3%).	USA	(47)
26	2021	From January to March 2020	Neonatal sepsis	57 *Burkholderia cepacia* isolates	CFPM (100%), CAZ (96.7%), COT (95%), CTX (90%), MRP (87%), TZP (85%), and LVX (20%) while high resistance (100%) was observed to amoxicillin-clavulanic acid, AMP-SUL, CFZ, cefalotin, cefuroxime, cefpodoxime, TCN, cefoxitin, TOB, AMK, CN, and IMP.	Yemen	(48)
27	2022	From 2015 to 2021	BSI and pulmonary infection in hematopoietic stem cell transplant patients	32 *Bcc* isolates	MRP (87.5%), COT (87.5%), CAZ (78.1%), MIN (62.5%), and Cefoperazone-sulbactam (59.4%).	China	(49)
28	2023	From 2005 to 2013	BSI	35 *Bcc* isolates	TZP (97.1%), CAZ (94.2%), MRP (91.4%), COT (82.8%), MIN (71.4%), LVX (65.7%), CHL (22.8%), and TCN (20%).	India	(50)

* TOB: tobramycin, CN: gentamicin, AMK: amikacin, ISP: isepamicin, CAZ: ceftazidime, COT: cotrimoxazole, CHL: chloramphenicol, MRP: meropenem, IMP: imipenem, DRP: doripenem, DOX: doxycycline, MIN: minocycline, LVX: levofloxacin, CIP: ciprofloxacin, MOX: moxifloxacin, AZT: aztreonam, TZP: piperacillin-tazobactam, TCC: ticarcillin-clavulanic acid, AMP-SUL: ampicillin-sulbactam, CAZ-AVI: ceftazidime-avibactam, CLZ-TAZ: ceftolozane-tazobactam, PIP-AVI: piperacillin-avibactam, IMP-REL: imipenem-relebactam, TMO: temocillin, CST: colistin, TGC: tigecycline, TCN: tetracycline, CFZ: cefazolin, CFPM: cefepime, CTX: ceftriaxone, BSI: bloodstream infection, UTI: urinary tract infection, RTI: respiratory tract infection, MIC: minimum inhibitory concentration, BIC: biofilm inhibitory concentration.

Table 2: Information retrieved from *in-vivo* studies

	Year	Study type	Sample size	Clinical diagnosis	Susceptibility (%)	Treatment	Duration	Outcome	Country	Ref.
1	2016	Case report	1	CF with chronic airway infection	Sensitive to CAZ, TMO, TZP, and MRP, intermediate-resistant to CIP, and AZT while resistant to AMK, CN, TOB, and CST.	IV TOB, CAZ, and TMO were used followed by inhaled TOB.	IV antibiotics (two weeks) followed by inhaled tobramycin (three months).	Successfully eradicated	UK	(51)
2	2016	Retros-pective study	22	Peritoneal dialysis patients with exit-site infection	CAZ (95.5%), TZP (95.5%), PIP (90.9%), and COT (81.8%) Resistance to aminoglycosides was (CN – 100%; AMK – 81.2%; TOB 81.9%), and to TCC (90.9%)	5 patients treated with only oral antibiotics (LVX n = 3; amoxicillin-clavulanic acid n = 1; cephalexin n = 1). 12 patients had oral, followed by IV antibiotics (CAZ n = 9; TZP n = 2; TCC n = 1). 5 patients only had topical treatment (0.05% chlorhexidine gluconate n = 4; 5.85% NaCl dressing n = 1).	The standard duration of antibiotic treatment was14 days	15 (68.2%) resolved with medical treatment (5 treated with oral, 5 with IV, and 5 with topical treatment).	Hong Kong	(52)
3	2017	Case report	1	Recurrent osteomyelitis and bacteremia	Sensitive to CAZ, MRP, COT, and TGC; intermediate-resistant to MOX; and resistant to AMK and CIP.	Initial treatment: IV CAZ for 14 days followed by oral COT and oral MOX for 3 months. IV TGC and IV COT twice daily as salvage therapy for 1 month after readmitting to the hospital.	14 days followed by 3 months then 1 month after recurrence	Recurrence after initial treatment but clinical condition improved after salvage therapy	Taiwan	(53)
4	2017	Pilot, open-label clinical trial	10	CF with chronic *Bcc* infection	not mentioned	Inhalation powder of tobramycin delivered by Podhaler	Twice daily for 28 days	Sputum bacterial density had a Mean drop of 1.4 log CFU/ml after 28 days.	Canada	(54)

	Year	Study type	Sample size	Clinical diagnosis	Susceptibility (%)	Treatment	Duration	Outcome	Country	Ref.
5	2017	Cohort study	248	Non-CF with *Bcc* BSI.	COT (94%), LVX (88%), CAZ (72%) and MRP (69%). TCC displayed poor activity (6%).	The definitive antibiotic therapy included fluoroquinolones in 35% (CIP [22%] and LVX [13%]), carbapenems in 20% (MRP [11%] and IMP [9%]), COT in 18.5%, TZP in 15%, and CAZ in 11% of cases. Combination therapy was used in 29% (73/248), with 39 different combinations. Of the 73 patients who received combination therapy, 43 (59%) were given fluoroquinolone-containing regimens, 25 (34%) carbapenem-containing regimens, 16 (22%) COT–containing regimens, and 13 (18%) CAZ-containing regimens.	Not mentioned	Survival rate was as follows for each antibiotic treatment: COT (19.3%), CAZ (11.8%), MRP (11.8%), IMP (8%), LVX (15%), CIP (23%), and Combination definitive therapy (27.8%).	USA	(19)
6	2018	Case report	1	Bacteremia with *Bcc*	The organism was susceptible to CAZ-AVI.	Continuous infusion with CAZ-AVI (50 mg/kg/dose IV, every 8 hours).	3 weeks	No further positive blood cultures.	USA	(20)
7	2018	Case report	1	Bacteremic pneumonia, following bilateral lung transplant in CF patient due to mixed infection with *Bcc* and *Pseudomonas aeruginosa*	Only susceptible to CAZ-AVI. Resistant to MRP, CLZ-TAZ, TZP, and MOX. Synergy was detected for MRP combined with CAZ-AVI.	The patient was treated with CAZ-AVI in extended infusion, and nebulized CST (for the treatment of *Pseudomonas aeruginosa* infection). In the ICU, MRP was added in extended infusion, and nebulized CST was increased in dose using a vibrating plate nebulizer.	26 days	Clinical improvement	Spain	(55)
8	2018	Case report	1	Neonatal infective endocarditis in non-CF	Sensitive to CFPM, CAZ, and MRP. Resistant to AMP, TZP, AMK, CN, CIP, COT, CEZ, and NFT.	A regimen of multiple antibiotics composed of AMP-SUL, CN, MRP, and CTX was initiated. IMP was included on the 12th day of admission.	Not mentioned	The patient was declared dead by cardiac arrest.	Indonesia	(56)
9	2018	Case report	1	*Burkholderia cepacia* keratitis	Sensitive to CAZ, MRP, and COT.	Topical CAZ was given intensively to the patient.	6 weeks	The infection resolved after treatment.	Southeast Asia	(57)

	Year	Study type	Sample size	Clinical diagnosis	Susceptibility (%)	Treatment	Duration	Outcome	Country	Ref.
10	2018	Case series	3	Nosocomial pneumonia after cardiac surgery	not mentioned	Patients 1 and 2: treated with CAZ and TOB. Patient 3: treated with CAZ.	Not mentioned	Patients 1 and 2 died of septic multi-organ failure & the third patient's condition improved steadily.	Germany	(58)
11	2018	Retros pective study	6	Chronic airway infection in CF	Multiple patient strains demonstrated pan-resistance based on *in-vitro* antibiotic sensitivity testing.	Induction period (21 days): IV TOB, IV CAZ, oral COT, and inhaled TOB. Consolidation period (2 months): oral COT, and inhaled TOB.	Induction period: 21 days. Consolidatio n period: 2 months.	Clearance of *Bcc* from sputum cultures.	USA	(59)
12	2019	Case report	1	CF	Sensitive to AZT, CAZ, CFPM, MRP, TMO, and COT. Resistant to AMK, CIP, CN, and TZP.	IV MRP and CAZ for 1 week, followed by IV CAZ and oral COT for another week then oral COT for a third week. Nebulized MRP was added at discharge. COT was stopped due to severe diarrhea and weight loss so oral LVX and MRP nasal lavage were started in addition to the nebulized MRP. After 1 month, the throat swab was still positive so nasal and nebulized TMO were combined with nasal and nebulized MRP and oral LVX.	9 months after the start of the last regimen.	The organism was successfully eradicated	Belgium	(60)
13	2019	Case report	1	Refractory bacteremia from consolidation pneumonia in non-CF	not mentioned	The successful antibiotic regimen was IV MRP and AMK, oral LVX and MIN, and MRP nebulization.	Bacteremia cleared on the 51st hospital day	Clinical improvement	Philippines	(61)

	Year	Study type	Sample size	Clinical diagnosis	Susceptibility (%)	Treatment	Duration	Outcome	Country	Ref.
14	2019	Retros pective study	4	CF with pulmonary exacerbation	All isolates were resistant to CAZ. *Burkholderia cenocepacia* was pan-drug-resistant. *Burkholderia vietnamiensis* was MDR. *Burkholderia multivorans* isolates were sensitive to IMP, TZP, and MIN while resistant to MRP, CAZ, AZT, and TOB.	CAZ-AVI-based therapy in combination with two or more antibiotics including MRP, COT, MIN, CHL, CIP, and TOB.	Ranged between 14 to 145 days.	Clinical improvement	UK	(62)
15	2019	Case report	1	CF with chronic airway infection. Followed by, bacteremia and multiple brain abscesses after lung transplant.	A high susceptibility to CAZ-AVI was detected. Intermediate-resistant to MRP and resistant to COT, CAZ, AMK, LVX, TZP.	IV antibiotic therapy with MRP and COT was prescribed. IV LVX was added on day 17 of admission to the hospital to MRP and COT. CAZ-AVI once daily after hemodialysis was added on day 19.	129 days	Blood culture resulted negative on day 26.	Italy	(22)
16	2019	Case report	2	CF with *Burkholderia cepacia* chronic infection and the other patient had *Burkholderia multivorans* chronic infection. Both had lung transplant.	*Burkholderia cepacia* was resistant to all fluoroquinolones, β-lactams, COT, TGC, and CHL but CAZ-AVI susceptibility testing yielded an MIC of 3 µg/mL. *Burkholderia multivorans* was susceptible to CN, TOB, DOX, and CAZ-AVI (MIC 2 µg/mL).	The first patient was treated with (CAZ-AVI + CIP + COT) for 3 weeks after surgery. The second patient was treated with CAZ-AVI as well as nebulized TOB for 15 days after transplantation.	3 weeks for the first patient. 15 days for the second	Death of the first due to uncontrolled intracranial invasion. The second patient had clinical improvement.	Spain	(63)

	Year	Study type	Sample size	Clinical diagnosis	Susceptibility (%)	Treatment	Duration	Outcome	Country	Ref.
17	2020	Retrospective study	216	Non-CF adult patients with *Bcc* bacteremia	COT (92.8%), TZP (90.3%), CAZ (75.5%), MRP (72.3%), LVX (64.1%), and TCC (11.8%)	The most frequently used definitive antibiotic was CIP (20.8%), then TZP (15.3%), MRP (13.7%), CAZ (13.7%), and CFPM (13.5%). Combination therapy was used with 12.6% of patients.	Not mentioned	30-day mortality rate was as follows: MRP (20.8%), TZP (20.8%), CAZ (16.7%), CFPM (8.3%), and combination therapy (8.3%).	South Korea	(64)
18	2020	Mouse Model	8	Chronic Lung Infection	LVX had MICs between 0.25 and 8mg/L. It was more active than AZT, TOB, or AMK.	Treatment with aerosolized LVX started 72h after infection. It was administered once or twice a day.	4 days	At least 1 log CFU of bacterial killing occurred against all tested strains.	USA	(65)
19	2020	Retrospective study	14	CF	The treatment matched the data of antibiogram in 50% of *Bcc*-infected patients. (Detailed results not mentioned)	All regimens of treatment were combinations of two or more antibiotics and composed of an IV beta-lactam in 8 cases, combined with an IV or inhaled aminoglycoside and/or IV CIP. Oral treatments (4 patients) included LVX or CIP and/or COT. Three patients had received inhaled AZT lysine.	14 days for IV treatment and 21 to 28 days for oral.	5 of the 10 treated cases, and 3 of the 4 untreated had cleared the *Bcc*.	France	(66)
20	2020	Case report	1	Endogenous endophthalmitis	Sensitive to MRP, LVX, and AMK.	IV MRP and oral LVX which was given for 7 days. MRP was injected inside the abscess and intravitreal injection of MRP and AMK were repeated every 72 hours.	Not mentioned	Clinical condition has improved with no recurrence of infection.	India	(67)
21	2020	Case report	1	*Burkholderia cenocepacia* keratitis	Sensitive to CAZ, CIP, MRP, MIN, and COT.	MOX 0.5% eyedrops hourly round the clock.	1 Month	The ulcer healed completely.	India	(68)
22	2021	Retrospective study	195	*Bcc* bacteremia in non-CF	COT (95.9%), MRP (75.4%), CAZ (74.4%), and LVX (25.1%).	Fluoroquinolone monotherapy (18%), COT monotherapy (6.7%), CAZ monotherapy (25.1%), MRP monotherapy (36.9%), and TGC monotherapy (5.1%). Combination therapy was used in 34.6%.	Not mentioned	No antimicrobial regimen was associated with significantly better outcomes.	Taiwan	(69)

	Year	Study type	Sample size	Clinical diagnosis	Susceptibility (%)	Treatment	Duration	Outcome	Country	Ref.
23	2021	Retrospective study	17	*Burkholderia cepacia* keratitis	CAZ (100%), MRP (94.1%) and COT (94.1%).	LVX, CAZ, and AMK were prescribed to 9 (52.9%), 6 (35.3%), and 2 (11.7%) patients, respectively.	Not mentioned	12 patients had good responses to treatment while surgical interventions were needed for 5 patients.	Taiwan	(70)
24	2022	Case report	1	Sepsis secondary to pneumonia in non-CF patient	Sensitive to MRP and LVX.	High-dose IV MRP, oral LVX, and inhalational AMK. LVX was stopped 4 weeks after therapy due to tenosynovitis concern. Oral double-strength COT was started.	9 weeks	The patient had good clinical condition and discharged from hospital after 54 days of admission.	United Arab Emirates	(71)
25	2022	Case Series	44	Bacteremia, vertebral osteomyelitis skin, and soft tissues infections.	CAZ (84.1%), TCN (54.5%), COT (63.2%) and carbapenems (65.9%). 3 out of the 8 isolates tested for quinolones susceptibility were resistant. 2 out of the 4 isolates tested for TZP susceptibility were resistant.	Directed antibiotic regimens including one or more of these antibiotics: CAZ, quinolones, COT, and carbapenems.	Average duration of 23 days	Patients responded well to therapy.	Lebanon	(72)
26	2022	Case report	1	Community-acquired pneumonia in a patient with pulmonary tuberculosis	Sensitive to CAZ, MRP, MIN, and COT.	MRP and MIN for 2 weeks and continued to use isoniazid and rifampicin for antituberculosis therapy.	2 weeks	Clinical improvement.	China	(73)

	Year	Study type	Sample size	Clinical diagnosis	Susceptibility (%)	Treatment	Duration	Outcome	Country	Ref.
27	2023	Case report	1	Sickle cell disease patient with peri-splenic intrabdominal abscess.	not mentioned	Treated with IV MRP with oral LVX for 14 days. Further treatment with oral COT as a long-term 'mopping up' agent was continued for a further 6 months.	Combination therapy: 14 days followed by monotherapy for 6 months.	Clinical improvement within two weeks.	India	(74)
28	2023	Murine model *in-vitro* and *in-vivo* study	425	Neutropenic murine lung infection model	Cefiderocol (94.8%) with MIC50/90 ≤0.03/0.5 µg/ml.	Lung infection of immunocompetent rat was used for the evaluation of the *in-vivo* activity of cefiderocol against *Burkholderia cepacia* ATCC 25416. Humanized doses were administered to achieve plasma concentrations corresponding with the free drug estimated plasma concentrations.	Dosing continued for a total of 96 h	Cefiderocol showed bactericidal activity.	Europe	(75)

* TOB: tobramycin, CN: gentamicin, AMK: amikacin, CAZ: ceftazidime, PIP: piperacillin, COT: cotrimoxazole, CHL: chloramphenicol, MRP: meropenem, IMP: imipenem, DOX: doxycycline, MIN: minocycline, LVX: levofloxacin, CIP: ciprofloxacin, MOX: moxifloxacin, AZT: aztreonam, TZP: piperacillin-tazobactam, TCC: ticarcillin-clavulanic acid, AMP-SUL: ampicillin-sulbactam, CAZ-AVI: ceftazidime-avibactam, CLZ-TAZ: ceftolozane-tazobactam, TMO: temocillin, CST: colistin, TGC: tigecycline, TCN: tetracycline, CFPM: cefepime, CTX: ceftriaxone, NFT: nitrofurantoin, BSI: bloodstream infection, IV: intravenous, MDR: multi-drug resistant, MIC: minimum inhibitory concentration.

to treatment with a combination of antibiotics previously mentioned as suggested for Bcc treatment (levofloxacin, ceftazidime, meropenem, minocycline, and cotrimoxazole) although other antibiotics were also included in the combination therapy as moxifloxacin and tigecycline that was reported as a successful salvage therapy with cotrimoxazole for recurrent osteomyelitis caused by *B. cepacia*[53], and amikacin antibiotic was also reported to be included in the combination therapy as intravenous for the treatment of bacteremia[61], intravitreal injection for endophthalmitis[67], or inhaled for a case of sepsis secondary to pneumonia[71]. Again, chloramphenicol wasn`t included in the treatment regimen in any of the included non-CF *in-vivo* studies. One case report of bacteremia caused by Bcc was treated with ceftazidime-avibactam continuous infusion (intravenous 50 mg/kg/dose, every 8 hours). It was noted that 24 hours after receiving the antibiotic, the patient had no further positive cultures from blood and remained free of infections with Bcc for 10 months later[20].

Two case studies reported poor outcomes of Bcc infections despite treatment. One for neonatal infective endocarditis non-CF patient received a multiple-antibiotic combination regimen composed of meropenem, ampicillin-sulbactam, ceftriaxone, and gentamicin. Imipenem was added on the 12th day of admission but still the patient was declared dead by cardiac arrest[56]. The other study reported 2 patients having nosocomial pneumonia after cardiac surgery, both treated with ceftazidime and tobramycin antibiotics but they died of septic multiorgan failure[58].

3.4. Consistency between *in-vivo* studies and *in-vitro* antibiotic susceptibility studies

The European Committee on Antimicrobial Susceptibility Testing (EUCAST) is not supporting testing for antimicrobial susceptibility against Bcc as a guideline in treatment due to the lack of a clear correlation between results of *in-vitro* susceptibility tests and the clinical outcomes of patients[87]. On the other hand, both the antibiogram committee of the Microbiology French Society and the Clinical and Laboratory Standards Institute (CLSI) provide guidelines for a limited number of antimicrobial agents. In agreement with Gruzelle *et al* study, we considered that the treatment matched the antibiogram when the bacterial isolate was sensitive to at least two antibiotics used in the treatment, or to one antibiotic when combined with tobramycin inhalation due to the high expected concentrations of local tobramycin[66]. Based on information retrieved from the *in-vivo* studies included in our review, 13 studies showed consistency between clinical condition outcomes after receiving treatment regimens and the performed *in-vitro* susceptibility testing, 7 studies either didn`t mention the antibiogram of the Bcc isolates or the antibiotics used for the treatment were not included in the susceptibility testing, one study showed inconsistency with low rates of survival although the antibiotics included in the regimen had high susceptibility rates[19] and one study showed no matching between the antibiogram and the treatment as the strains were pan-resistant but the treatment protocol was successful in eradicating the pathogen[59].

In the study of Desmond *et al*, the antibiotics used for oral treatment were not included in the susceptibility testing so matching and consistency couldn`t be determined while those used for systemic treatment of 12 patients were included in susceptibility testing and only 5 patients showed a favorable response[52]. On the other hand, the case study presented by Yonas *et al* declared the death of the neonatal infective endocarditis patient but the treatment regimen didn`t match the antibiogram and 3 of the antibiotics included in the treatment weren`t mentioned in the susceptibility testing[56]. Similarly, in the 2 case reports presented by Los-Arcos *et al*, the first patient's treatment didn`t match the antibiogram and the patient died from uncontrolled intracranial invasion while the second patient showed matching between treatment and antibiogram accompanied by clinical improvement showing consistency between the clinical condition outcome after receiving treatment regimen and the performed *in-vitro* susceptibility test[63]. In the retrospective study performed by Gruzelle *et al*, there was a match between treatment and antibiogram data in 50% of Bcc-infected patients and out of them 80% showed consistency in outcome (eradication achieved)[66]. Aerosolized levofloxacin was tested *in-vivo* in a mouse model of chronic lung infection caused by *B. cepacia* isolates from CF patients. At least 1 log CFU of bacterial killing against all tested strains was achieved and this was largely consistent with the *in-vitro* results which showed that levofloxacin MICs for the tested strains were in the range between 0.25 and 8 mg/L along with the fact that it was more active against these isolates than amikacin, tobramycin, or aztreonam[65]. Consistency between the *in-vitro* and *in-vivo* activity was noted in another investigation conducted on a murine model testing the siderophore antibiotic cefiderocol antibacterial activity[75].

Analysis of the *in-vitro* studies revealed that cotrimoxazole (the first-line treatment of Bcc infections) was reported to be amongst the antibiotics

having the highest susceptibility rates in 9 studies out of 20 that included this antibiotic in susceptibility testing. In three different studies out of the 9, cotrimoxazole was equivalent in susceptibility rate to ceftazidime in one of them[24], and equivalent to meropenem in another two studies[36,49]. It had 100% susceptibility in 2 studies[24,27]. It was reported second to meropenem and equivalent to ceftazidime in susceptibility in one study[31]. Two studies reported it second to ceftazidime[28,46] where it was equivalent to levofloxacin and minocycline in one of them[28]. It was second to levofloxacin in Demirdag *et al* study[42]. In Papp-Wallace *et al* study, it was reported third in susceptibility after ceftazidime-avibactam then ceftazidime[32] while it came third after piperacillin-tazobactam then ceftazidime in Gautam *et al* study[41] and also third to cefepime then ceftazidime in Salah *et al* study[48]. On the other hand, in a study conducted by Cipolla *et al*, it was reported that the highest level of resistance was for cotrimoxazole[34]. Moreover, Kenna *et al* reported that resistance to cotrimoxazole, ceftazidime, piperacillin-tazobactam, ciprofloxacin, and minocycline was variable across the species of Bcc[29]. From the antibiotics that were tested for susceptibility against Bcc and weren`t included in the CLSI suggested antibiotics for testing and reporting of results against this pathogen, piperacillin-tazobactam and cefepime. Piperacillin-tazobactam was observed to have the highest susceptibility in 3 studies[29,41,50] while cefepime had 100% susceptibility in one study[48]. Out of the included *in-vivo* studies, 11 reported the use of cotrimoxazole in the treatment regimens mostly in oral formulations and in combination with other antibiotics or as a long-term oral therapy following the IV treatment. Singh *et al* recommended the use of cotrimoxazole as a long-term "mopping up" agent[74]. Abbott *et al* reported that the most common combinations showing synergism were tobramycin combined with ceftazidime, meropenem combined with tobramycin, and levofloxacin combined with piperacillin-tazobactam (35.4%, 32.3% and 22.2% synergy, respectively)[26]. A fact that was used in the *in-vivo* studies where 3 studies reported the use of tobramycin inhalation or intravenous in combination with different antibiotics and another study reported the use of aminoglycosides in general in the combinations used for treatment. El-Halfawy *et al* reported that upon adding colistin in low doses, the efficacy of the tested combination of moxifloxacin and ceftazidime was improved[33].

The novel ceftazidime-avibactam antibiotic was reported as the most potent in 2 studies and second in susceptibility to cotrimoxazole in one study. In relation with the *in-vivo* studies, 4 case studies had ceftazidime-avibactam as a part of their treatment strategy and only one study reported patient death after a treatment regimen of ceftazidime-avibactam combined with ciprofloxacin and cotrimoxazole for 3 weeks. Of the novel antibiotics included in the *in-vitro* susceptibility testing, cefiderocol, ceftolozane-tazobactam, imipenem-relebactam, and piperacillin-avibactam all reported high susceptibility rates except one study reported resistance of tested isolates against ceftolozane-tazobactam[37]. No *in-vivo* studies included in the review had mentioned these antibiotics except cefodrocol which was tested for activity using a murine model[75].

3.5. Treatment duration

Duration of therapy was mentioned in 21 *in-vivo* studies out of the 28 included. A total of 9 focused on CF patients, 10 were for non-CF patients, and 2 were murine models. In the 9 studies of CF patients, the duration of treatment ranged between a minimum of 2 weeks[62] to 9 months[60]. The treatment regimens for CF patients included in the review combined systemic treatment in addition to oral and/or inhaled treatment mostly had a duration of 2[51,66] or 3 weeks[59] for the systemic therapy while long duration of treatment was noticed for oral and/or inhaled treatment, to be 1[66], 2[59], 3[51], or 9 months[60]. A review article focused on CF patients with Bcc infections reported that the treatment duration varied widely from 2 weeks to 6 months. They also reported that a minimum treatment duration with antibiotics for CF patients has been recommended to be 10 days. Two weeks of treatment are standard at many centers[88]. Randomized studies with CF patients do not support a specific duration of treatment. As a result, the physicians must evaluate each patient separately, considering their own experiences, prior clinical outcomes, and *in-vitro* antibiotic susceptibility data[89]. Additionally, the goal of antimicrobial treatment would have a major role in determining how long the course of treatment would last. Attempts to manage or eradicate empyema might require prolonged medical care[88]. The Bcc eradication protocol for CF patients implemented by Garcia *et al* had 2 stages of treatment, an induction period of 21 days and a consolidation period of 2 months[59]. On the other hand, the 10 *in-vivo* studies that were focused on non-CF patients had a duration of treatment ranging between a minimum of 2 weeks[52], as previously noticed in CF studies to 6 months[74]. Two studies reported treatment in non-CF patients in 2 stages, the first was maintained for 2 weeks while the second had a longer duration of 3 months[53] or 6 months[74]. Both were case studies, one of them was for a patient with recurrent osteomyelitis

and bacteremia while the other was for a patient with sickle cell anemia having an intraabdominal peri-splenic abscess. Singh *et al* recommended a combination therapy of synergistic antimicrobial compounds followed by long-term treatment with oral cotrimoxazole[74]. Niyas *et al* reported that parenteral and inhaled antibiotics along with corticosteroids are required for the treatment of sepsis secondary to Bcc-caused pneumonia. It is necessary to define the duration of therapy, type, and dosage of treatment combination in advance. These factors might vary according to the patient[71].

4. CONCLUSION

The species of Bcc are opportunistic pathogens that most commonly infect persons with CF or compromised immune systems. They are intrinsically multidrug-resistant so treating infections brought on by this pathogen can be challenging. Extracting and analyzing the data from *in-vitro* and *in-vivo*/clinical research during the past ten years is the goal of our review. The results of the analysis were used to identify possible perspectives along with reported durations needed for the treatment of infections in both CF and non-CF patients. Notably, most research conducted in the past ten years has been focused on Bcc infections in non-CF patients with the majority having bloodstream infections. Protocols used for treatment mostly depended on combination therapy in both CF and non-CF-infected individuals. The most frequently used intravenous antibiotics were ceftazidime either alone or combined with avibactam and meropenem while the most frequently used oral antibiotics were cotrimoxazole and fluoroquinolones, particularly levofloxacin. These 4 antibiotics were included in CLSI 2024 guidelines of antimicrobial agents suggested for reporting and investigation against Bcc. The other agent included in the guidelines was minocycline, which was included in only 2 case reports of non-CF patients in addition to one retrospective study of CF patients. Other antibiotics that were not suggested for treatment or investigation against the Bcc but were noted to be frequently used in the combination regimens were the aminoglycosides usually tobramycin and amikacin. Treatment for Bcc infections needs to be customized according to the culture outcome. Analysis of *in-vivo* studies that mentioned both the antibiogram and treatment regimen, revealed that the majority of the regimens matched the *in-vitro* antibiogram and only one study was accompanied by inconsistent outcomes having low survival rates. The novel cefiderocol antibiotic can be considered as a promising potential area for additional studies as it was accompanied by a high *in-vitro* susceptibility rate in addition to the significant bactericidal activity noted in the murine model *in-vivo* study although it wasn`t included in any of the clinical *in-vivo* studies. The other antibiotic that can be considered an ideal target for additional studies is ceftazidime-avibactam which was reported as a potent antimicrobial agent in both *in-vitro* and *in-vivo* studies so further investigation of novel combinations or antibiotic adjuvants that can enhance its activity and decrease resistance is also a promising potential area of research.

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