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REVIEW

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Cepacia syndrome in cystic fibrosis: A systematic review of the literature and possible new perspectives in treatment

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Abstract

Background: Cepacia syndrome (CS) is an acute, necrotizing pneumonia with a high mortality rate, occurring in patients with cystic fibrosis (CF) infected with *Burkholderia cepacia* complex (BCC). Due to its low incidence, data on this condition are limited.

Methods: We conducted a systematic review of the reported cases of CS by searching MEDLINE, Embase and the Cochrane Library to improve knowledge of this rare but potentially lethal condition.

Results: We included 15 eligible articles, describing 18 cases (9 females) of CS. Median age at onset was 22 years (range: 10–60 years); median time to CS after first infection by BCC was 5 years (range: 1–26 years). *Burkholderia cenocepacia* was the most frequently reported causative agent. All patients received intravenous antibiotic treatment (most frequently including cotrimoxazole), while inhaled antibiotics were used in five patients (27.8%). Immunosuppressant agents were the most commonly prescribed supportive treatment ($n = 7$, 38.9%). Half of the patients died (9/18, 50%).

Conclusions: This study describes epidemiological, clinical characteristics, and prognosis of CS cases reported over the last 24 years. CS is a rare yet severe complication of BCC infection in patients with CF, which occurs several years after BCC colonization and has a negative outcome in 50% of the patients. Data are too scanty to identify the most effective therapeutic approach.

KEYWORDS

Burkholderia cepacia, cepacia syndrome, cystic fibrosis, cytokine storm syndrome

1 | BACKGROUND

Cepacia syndrome (CS) is an acute, necrotizing pneumonia with elevated mortality rate, characterized by high fever, bacteremia, and rapidly progressive respiratory failure, occurring in patients with cystic fibrosis (CF) infected with *Burkholderia cepacia* complex (BCC) bacteria.[1] The incidence of CS is largely unknown but it is expected to have declined due to the strict patient segregation policy adopted by CF centers, that has reduced the prevalence of BCC colonization.[2] BCC encompasses at least 22 closely related bacterial species.[3]

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Burkholderia cenocepacia and particularly the IIIA subgroup electrophoretic Type-12 or ET12 epidemic strain has been most frequently associated with CS.

Due to its low incidence, there is a lack of reliable evidence about this potentially fatal condition and on the optimal treatment regimen to adopt. Therefore, we conducted a systematic review of cases of CS reported in CF patients over the last decades, to identify potential factors contributing to the poor outcome and the most effective therapeutic approach.

2 | METHODS

We searched MEDLINE, Embase, and the Cochrane Library databases for original articles published in English up to September 14, 2021, regarding CS.[4–18] All original articles including case reports of CS were considered in this systematic review, while reviews, laboratory studies based on in vitro or animal models were excluded.

Citations were exported from the databases and then imported to Rayyan for title and abstract screening.[19] The following search terms were used: "cystic fibrosis" AND "cepacia syndrome."

Titles and abstracts were screened, and the full texts of the eligible articles were obtained. The references included in the full text of the eligible articles were manually searched to detect studies that could have been missed. From the included articles, we extracted the following data: year of publication, age of the patients, CF transmembrane conductance regulator (CFTR) genotype, BCC strain, time from infection to CS, body mass index (BMI), comorbidities, forced expiratory volume in 1 s (expressed as percentage of the predicted value [ppFEV]) measured before CS, white blood cell count (WBC), neutrophil count, C-reactive protein (CRP), blood cultures, pathogens isolated in sputum, prescribed treatment (antibiotic therapy and immunosuppressant agents) and outcome. The study findings were reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[20]

3 | RESULTS

The systematic search yielded 128 unique items; 114 were excluded: 57 were laboratory studies, 21 were not relevant for the study topic, 8 did not include patients with CF, 14 were reviews on the topic and 14 were conference proceedings. To the 14 items selected,[4–6,8–18] another one was added by manually searching the references of the articles identified during the electronic search.[7] A total of 15 articles were then included and summarized in this systematic review.

Table 1 gives a summary overview of the characteristics of the 18 cases of CS in CF patients, reported in the 15 selected articles.[4–18] Genotype was severe in all the 11 patients in whom it was available, and all of them carried at least one F508del mutation, 8 in homozygosity.

Median age at onset of CS was 22 years (range: 10–60 years), and this condition occurred after a median time from first infection by BCC of 5 years (range 1–26 years).

Burkholderia cenocepacia was the most commonly reported causative agent (11 cases), while other BCC species were less frequently described (*Burkholderia multivorans* in 3 cases, *Burkholderia vietnamiensis* in 1 case, and *Burkholderia ambifaria* in 1 case).

WBC highlighted leukocytosis with a shift to the left in most patients; CRP, when reported (five cases), was elevated.

Blood cultures were performed in 13 patients at different time points and confirmed the presence of BCC bacteremia in 11 patients (84.6%). Bacteremia was identified in the preterminal phase in 38% of cases.

Information on nutritional status and presence of comorbidities was very limited, being reported in less than 30% of the patients. ppFEV was measured in 10 patients, with values ranging from 31% to 101%. Two patients with ppFEV < 40% did not survive CS.

Table 2 reports the treatment received by each patient and the corresponding outcome. Intravenous (IV) antibiotic treatment, based on the results of the in vitro susceptibility tests, was undertaken in all patients. Cotrimoxazole (trimethoprim-sulfamethoxazole) was the most frequently administered antibiotic. Inhaled/nebulized antibiotics were prescribed in 5/18 patients, all of whom survived CS. Immunosuppressant agents, including oral or IV steroids, tacrolimus and cyclosporin, were the most commonly prescribed supportive treatments, administered in 7 out of the 18 considered cases. One patient, carrying the G551D mutation, was additionally treated with ivacaftor.

Overall, 9 out of 18 patients died due to CS with a case fatality rate of 50%. Case fatality rate was lower among females (33.3% as compared to 66.6% in males).

4 | DISCUSSION

Our systematic review identified 15 case reports, describing a total of 18 patients with CF and CS between 1998 and 2021.

The low number of reported cases may reflects the reduction in spread of transmissible BCC strain among patients with CF observed since the second half of 1990s.[21,22] This reduction has continued in more recent years with data from the CF Foundation Patient Registry showing a 3% annual decrease in incidence and prevalence of BCC infections in the period 2006–2012.[23] However, given the low frequency of BC, the link between this condition and the reduction in the spread of BCC has not been proven.

B. cenocepacia and *B. multivorans* were the most prevalent strains triggering CS, being responsible for 11 and 3 of the CS cases, respectively. These strains are commonly considered the most virulent. In fact, *B cenocepacia*, and in particular the ET12 epidemic strain is highly drug resistant and is associated with a fivefold higher mortality, compared to the other strains.[24]

No sex difference in reported cases were detected, while a poorer outcome was observed in males. Our data also suggest a possible relationship between CFTR genotype and occurrence of CS, as all the patients for whom genotype was reported carried severe mutations, including at least one copy of F508del mutation.

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TABLE 1 Characteristics of the 18 cases of cepacia syndrome reported in the 15 selected articles.

Case number	Reference	Age (year), sex	CFTR genotype	Comorbidities	BCC	Time elapsed from BCC infection to CS (years)	BMI (kg/m^2)	FEV1% predicted (before CS)	WBC/ neutrophilia	CRP (mg/L)	BCC in blood cultures (Pos/Neg)	Other pathogens isolated in sputum
1	Ledson et al.[4]	18, M	F508del/ F508del	NR	*B. cenocepacia*	4	NR	NR	NR	NR	NR	NR
2	Ledson et al.[4]	34, M	F508del/ F508del	NR	NR	4	NR	NR	NR/Yes	NR	NR	NR
3	Ledson et al.[4]	20, M	F508del/ F508del	NR	*B. cenocepacia*	NR	NR	NR	NR/Yes	NR	NR	NR
4	Dobbin et al.[5]	30, F	NR	NR	*B. cenocepacia*	2.5	NR	31	Yes/Yes	NR	Pos	*Pseudomonas* spp., *Haemophilus* influenzae, yeasts
5	Kazachkov et al.[6]	11, F	F508del/ F508del	NR	*B. cenocepacia*	1	NR	45	Yes/Yes	NR	Pos	-
6	Zahariadis et al.[7]	60, M	F508del/ Unknown	CFRD, nephropathy	*B. multivorans*	6	NR	NR	Yes/NR	NR	Pos	*Staphylococcus aureus*, *Acinetobacter baumanii* complex
7	Blackburn et al.[8]	16, M	F508del/ F508del	NR	*B. multivorans*	9	NR	70	NR/Yes	190	Pos	*Pseudomonas aeruginosa*
8	George et al.[9]	40, M	NR	NR	*B. cenocepacia*[a]	NR	22.9	38	Yes/NR	-	Pos	-
9	Hindo et al.[10]	15, F	NR	ABPA	*B. cenocepacia*	1.4	NR	NR	Yes/NR	NR	Pos	Alfa-hemolytic streptococci, *Neisseria* spp., MSSA, nontypeable *H. influenzae*, *Serratia marcescens*, *Aspergillus* spp.
10	Weidmann et al.[11]	31, F	NR	Type 1 DM, CFRLD	*B. cenocepacia*	16	18.4	48	Yes/NR	234	Neg	-
11	Grimwood et al.[12]	10, F	F508del/ F508del	NR	*B. cenocepacia*	1	NR	101	Yes/NR	113	Pos	MSSA, *Hemophilus influenzae*
12	Nash et al.[13]	24, M	NR	None	*B. cenocepacia*	NR	NR	NR	NR	NR	Pos	NR
13	Nash et al.[13]	30, F	NR	Chronic malnutrition, CFRD	*B. cenocepacia*	19	NR	NR	NR	NR	Pos	NR
14	Nash et al.[14]	17, F	F508del/ F508del	ABPA, CFRD	*B. cepacia*	7	25.8	101	NR	NR	Pos	-

(Continues)

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TABLE 1 (Continued)

Case number	Reference	Age (year), sex	CFTR genotype	Comorbidities	BCC	Time elapsed from BCC infection to CS (years)	BMI (kg/m^2)	FEV1% predicted (before CS)	WBC/ neutrophilia	CRP (mg/L)	BCC in blood cultures (Pos/Neg)	Other pathogens isolated in sputum
15	Shafiq et al.[15]	18, F	F508del/ N1303K	NR	*B. multivorans*	4	NR	43	NR	NR	NR	NR
16	Gilchrist et al.[16]	38, M	F508del/ F508del	NR	*B. cenocepacia*	26	NR	49	Yes/Yes	279	Neg	*Candida albicans*
17	Castro-Elias et al.[17]	12, M	F508del/ G551D	Chronic malnutrition, CFRD	*B. vietnamiensis*	6	16.1	>50	Yes/Yes	4.4	NR	MSSA, *Klebsiella pneumoniae*, mucoid *P. aeruginosa*, Rhinovirus
18	Goodlet et al.[18]	41, F	NR	NR	*B. ambifaria*	NR	NR	NR	Yes/No	NR	Pos	NR

Abbreviations: ABPA, allergic bronchopulmonary aspergillosis; BCC, Burkholderia cepacia complex; BMI, body mass index; CF, cystic fibrosis; CFRD, CF-related diabetes; CFRLD, CF-related liver disease; CRP, C-reactive protein; CS, cepacian syndrome; DM, diabetes mellitus; F, female; FEV1, forced expiratory volume in the 1st s; M, male; MSSA, methicillin-sensitive Staphylococcus aureus; NR, not reported; Pos, positive; Neg, negative; WBC, white blood cell count.

[a]According to local epidemiology: genomovar III was suspected.

CS has previously been thought to occur shortly after the first isolation of BCC.[5] Our systematic review does not confirm this hypothesis, as in the reported cases, CS occurred around 5 years after BCC first infection.

In contrast, it was not possible to establish an association between CF comorbidities (particularly allergic bronchopulmonary aspergillosis and CF-related diabetes) and the onset of CS, as the presence of these underlying conditions was not reported in most of the papers included in our systematic review.

In the analyzed cases, quite different therapeutic options were used, both in terms of type of antibiotics chosen for nebulization as well as in terms of supportive treatments associated with antimicrobial agents (immunosuppressant agents in two cases, inhaled rhDNase in one case and ivacaftor in one case carrying the G551D mutation). With regard to antibiotic treatment, our review suggests a positive effect of a combination of intensive IV and nebulized antibiotics regimen on the outcomes of CS, as this treatment was prescribed in 5/18 patients and all of them survived. Experience in the use of inhaled antibiotics in CS is mainly derived from cases sustained by *B. cenocepacia*; however, this therapeutic approach was also successfully applied to one patient infected by *B. vietnamiensis* and to another infected by *B. ambifaria*. However, the better outcome observed in some patients receiving a combination of inhaled and IV antibiotics rather than additional IV antibiotics may be related to a less severe disease among the former group of patients.

Given the limited number of cases reported and the difficulty in conducting a randomized clinical trial in such a rare condition, the actual efficacy of inhaled antibiotics remains uncertain. New evidence in this regard can only be gathered from a systematic collection of new cases.

The pathogenesis of BCC infection in CF relies on the interplay between microbial virulence factors and host immune response. *B. cenocepacia* strains expressing both cable pili and associated 22 kDa adhesin are able to transmigrate through the airway epithelium and mucin.[25] Another mechanism used by bacteria involves the activity of the alternative RNA polymerase extracytoplasmic sigma factor, an important regulator of the extracytoplasmic response that promotes the intracellular survival of *B. cenocepacia*, delaying phagolysosomal fusion in macrophages.[26] Furthermore, BCC forms biofilms, which can protect from both host defenses and antibiotics, and have a distinct lipopolysaccharide that has also been implicated in resistance to antibiotics and antimicrobial peptides.[27] In addition, BCC secretes a number of factors, such as catalases, proteases and siderophores, which can help BCC to evade the host's defenses.[28] However, the contribution of single factors to the overall virulence of BCC in CF remains to be better defined. In CS, BCC lipopolysaccharides are known to induce a remarkable release of pro-inflammatory cytokines (interleukin [IL]-6, IL-8, tumor necrosis factor-α) by the respiratory epithelium, four- to eightfold higher than other Gram-negative pathogens, thus stimulating a significant neutrophil mediated inflammatory response.[29] Once the infection is established, the prolonged and excessive local and systemic inflammation may lead to additional tissue damage, which becomes independent from the

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TABLE 2 Treatment received and outcome of the 18 cases of cepacia syndrome reported in the 15 selected articles.

Case number	Reference	Age (years), sex	Antibiotic treatment	Other treatments	Outcome
1	Ledson et al.[4]	18, M	IV: cotrimoxazole, colistin, piperacillin	-	Died
2	Ledson et al.[4]	34, M	IV: ceftazidime, tobramycin. colistin, ceftazidime, co-trimoxazole PO: chloramphenicol	-	Died
3	Ledson et al.[4]	20, M	IV: cotrimoxazole, colistin, ceftazidime	-	Died
4	Dobbin et al.[5]	30, F	IV: cefepime, tobramycin, meropenem, ciprofloxacin, cotrimoxazole, ticarcillin-clavulanate	steroids, itraconazole	Died
5	Kazachkov et al.[6]	11, F	IV: ceftazidime, meropenem, ciprofloxacin, choloramphenicol, cotrimoxazole	IV: methyl-prednisolone	Survived
6	Zahariadis et al.[7]	60, M	IV: cotrimoxazole, ceftazidime, piperacillina-tazobactam, vancomycin	-	Died
7	Blackburn et al.[8]	16, M	IV: tobramycin, piperacillin-tazobactam, teicoplanin	IV: fluconazole, amphotericin	Died
8	George et al.[9]	40, M	IV: tobramycin, piperacillin/tazobactam, meropenem, ceftazidime	-	Died
9	Hindo et al.[10]	15, F	IV: ticarcillin/clavulanate, tobramycin, cotrimoxazole, meropenem, amikacin, ceftazidime	IV: amphotericin B, voriconazole, IV corticosteroids	Died
10	Weidmann et al.[11]	31, F	IV: meropenem, cotrimoxazole, tobramycin, temocillin Nebulized: meropenem, tobramycin	tacrolimus, mycophenolate mofetil	Survived
11	Grimwood et al.[12]	10, F	IV: ceftazidime, tobramycin, cotrimoxazole Nebulized: tobramycin	Nebulized: dornase alpha	Survived
12	Nash et al.[13]	24, M	IV: ticarcillin/clavulanate, meropenem, amikacin Inhaled: amikacin, colistin	PO: prednisone, tacrolimus	Survived
13	Nash et al.[13]	30, F	IV: meropenem PO: ciprofloxacin, azithromycin, doxycycline	-	Survived
14	Nash et al.[14]	17, F	IV: ceftazidime meropenem temocillin, tobramycin, metronidazole, flucloxacillin PO: ciprofloxacin, azithromycin, metronidazole	IV: hydrocortisone, PO: oseltamivir	Died
15	Shafiq et al.[15]	18, F	NR	NR	Survived
16	Gilchrist et al.[16]	38, M	IV: tobramycin, meropenem, cotrimoxazole, chloramphenicol	IV/PO cyclosporine, PO prednisolone, oseltamivir	Survived
17	Castro-Elias et al.[17]	12, M	IV: nafcillin, minocycline, ceftazidime, colistin, cotrimoxazole, chloramphenicol, cefotaxime Inhaled: tobramycin	ivacaftor	Survived
18	Goodlet et al.[18]	41, F	IV: minocycline, ciprofloxacin, ceftazidime/avibactam Inhaled: meropenem, tobramycin	-	Survived

Abbreviations: F, female; IV, intravenous; M, male; NR, not reported; PO, per os.

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pathogen itself. Indeed, the inflammatory cascade, originally aimed at infection control, may become responsible for the progression of lung tissue damage. This pathogenic mechanism, as well as other clinical features of CS, overlaps with another potentially life-threatening inflammatory condition known as cytokine storm syndrome (CSS), an umbrella term encompassing several disorders of immune regulation. CSS is characterized by elevated circulating cytokines levels, acute systemic inflammation and immune-cell hyperactivation leading to constitutional symptoms and secondary multiorgan dysfunction. CSS can be triggered by various pathogens (including SARS-CoV-2 infection), therapies, cancers, and other conditions targeted with immune-directed therapies, such as autoimmune disorders, primary and secondary hemophagocytic lymphohistiocytosis (HLH).[30] Secondary HLH may complicate different systemic diseases, most frequently infections. Cases of secondary HLH have been described in three patients with CF and were, respectively, induced by Nocardia, A/H1N1 influenza, and Adenovirus.[31-33] It is interesting to note that BCC septicemia and macrophage activation syndrome (MAS)/HLH are rare but well-known complications of chronic granulomatous disease (CGD) and four cases triggered by BCC have previously been described in this context.[34-36] Some of the pathophysiology of CS could potentially be compared to unrecognized MAS/HLH. Furthermore, HLH therapy consists in an aggressive treatment of the triggering event (infection or malignancy), associated with the use of immunosuppressant agents (IV steroid pulses, IV immunoglobulin, and/or cyclosporin).[37] In a non-CGD setting, such as in CF, immunomodulation might play a key role in the effective treatment of this condition. Of note, half of the patients who survived CS in the considered reports had been treated with immunosuppressant agents, in association with IV and/or inhaled antibiotics. Although the initial drivers of CSS may differ, late stage clinical manifestations seem to converge and overlap. Nearly all patients present with fever that may be of high grade, markers of inflammation are elevated and correlate with disease activity. All patients with CS in our review had fever, leucocytosis or neutrophilia were present in 13/18 cases, and CRP was increased in four of the five patients in whom it was measured.

When interpreting our results, it should be noted that they rely on published reports and are then prone to underreporting. In fact, our electronic search may have missed some CS cases, in particular, those who died after becoming infected with BCC but who have been not reported as CS cases.[38,39] On the other hand, patients with rapid decline of pulmonary function, but without the full clinical manifestations of CS may have been reported as CS, especially in the past.[7] Accurate determination of incidence and risk factors would require data from multicentre studies or from registries able to capture this information.

In conclusion, our systematic review confirms that CS is a rare yet severe complication of BCC infection in patients with CF, mainly triggered by *B. cenocepacia*. We found that this complication does not occur early after BCC infection and has a negative outcome in half of the patients. All patients carried at least one F508del mutation, thus it is possible that treatment with highly efficient CFTR modulators may also change CS occurrence and prognosis.

AUTHOR CONTRIBUTIONS

Valeria Daccò: Conceptualization; writing—original draft. **Gianfranco Alicandro**: Conceptualization; methodology; formal analysis; writing—review and editing. **Alessandra Consales**: Data curation; writing—review and editing. **Chiara Rosazza**: Data curation; visualization. **Calogero S. Sciarrabba**: Visualization; data curation. **Lisa Cariani**: Writing—review and editing. **Carla Colombo**: Writing—review and editing; Supervision.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

All data that support the findings of this study are available in the original publications.

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