ORIGINAL ARTICLE

Trend of isolation of *Burkholderia cepacia* complex bacteremia between 2008-2021: Insights from a major Pakistani laboratory network

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ABSTRACT

Background: *Burkholderia cepacia* complex (BCC) is an opportunistic pathogen, primarily affecting neonates and immunocompromised patients. Limited data exist in Pakistan on its prevalence and resistance patterns. This retrospective study aimed to assess trends of BCC infection and antimicrobial resistance from 2008 to 2021.

Material and Methods: This retrospective study analyzed trends of *Burkholderia cepacia complex* (BCC) infections and their antimicrobial resistance at Aga Khan University Hospital, Pakistan, from 2008 to 2021. Antimicrobial susceptibility was tested using the Kirby–Bauer disc diffusion method against chloramphenicol, ceftazidime, ciprofloxacin, minocycline, meropenem, trimethoprim-sulfamethoxazole, and tetracycline, and interpreted per CLSI guidelines. Data were processed in SPSS version 19.0, with frequencies and percentages calculated to assess laboratory-confirmed BCC cases.

Results: A total of 5411 BCC strains were isolated from blood cultures during a period of 2008–2021. We observed that neonates were the predominant age group (47-76%) almost each year for BCC bacteremia. This study observed highest resistance (up to 37%) in BCC strains against levofloxacin, isolated from both in-patients and out-patients. Higher meropenem resistance (37%) was found in in-patients isolates while 25% in out-patient isolates while ciprofloxacin resistance was higher (29% vs 20%) in outside referral blood cultures.

Conclusions: Continuous surveillance of *Burkholderia cepacia* complex (BCC) antibacterial resistance is essential to monitor the spread of resistance, as antimicrobial resistance imparts a very crucial role in the spread of infection to susceptible group.

Keywords: B. cepacia complex (BCC), Antimicrobial resistance, Neonates, Sepsis.

BACKGROUND

Burkholderia cepacia (*B. cepacia*), formerly known as *Pseudomonas cepacia* is a Gram negative, aerobic, non-fermenting bacillus. *B. cepacia* complex (BCC) comprises of at least 20 different species, that are catalase and oxidase positive, and inherently resistant to first and second generation cephalosporins, amoxicillin/ clavulanate, ertapenem, fosfomycin and polymyxins; resistance to third generation cephalosporins, trimethoprim and aminoglycosides is observed but not yet proven to be intrinsic.[1] BCC is mostly found in soil and moist environments and has an ability to grow in nutrient poor conditions and has emerged as an opportunistic pathogen where it mostly colonizes neonates or patients whose immune responses are compromised or who have other comorbid conditions.[2, 3] Infections caused by BCC ranges from superficial to deep-seated and disseminated while the most dramatic clinical presentation is septicaemia where patient presents with fever, severe progressive respiratory failure, high leukocyte counts and bacteremia and is associated with increased morbidity and mortality.[4]

Outbreaks of BCC infections from bloodstream, respiratory tract, and urinary tract have been reported in hospital settings.[5] In the United States, between the period of 2017-2018, several cases of BCC related infections were reported to the CDC which were found to be linked to a no rinse cleansing foam product.[6] Another study in India in the same period revealed a high mortality rate (47%) from BCC infections acquired from the hospital, without identification of a single source.[7] A study done in a hospital in Turkiye also reported a nosocomial outbreak of *B. cepacia* between the period of October 2022 and December 2023, which

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lasted approximately 270 days, while another one in 2024 found the culprit to be contaminated respirators.[8, 9]

Owing to the intrinsic resistance profile of BCC, its treatment options are limited.[10] Also, BCC has a contrasting antimicrobial susceptibility pattern to *P. aeruginosa*[11], hence correct identification and appropriate antimicrobial susceptibility testing is essential. Since antibiotic resistance is a global problem[12], information of drug susceptibility pattern is important as this has implications in choosing empiric treatment for suspected cases. The CLSI recommends testing BCC isolates against ceftazidime, meropenem, minocycline, and trimethoprim-sulfamethoxazole with Kirby Bauer disc diffusion method and against levofloxacin and ticarcillin-clavulanate by calculating the MIC.[13]

In Pakistan, data regarding the prevalence of BCC bacteremia and its susceptibility profile is limited [14-17]. This study was therefore designed to determine the frequency of BCC isolation from blood cultures submitted at Aga Khan Clinical Laboratories, and to observe antibiotic susceptibility pattern in strains isolated in different age groups of patients admitted in countrywide healthcare centres. This study would be helpful in refining approaches for controlling antimicrobial resistance.

MATERIAL AND METHODS

A descriptive retrospective review of laboratory records of blood culture positive cases of BCC was performed during the period of Jan 1st, 2008 – Dec 31st, 2021. All blood cultures requested within the study duration, with isolation of *Burkholderia cepacia* complex were included in the study. BCC culture negative specimens and duplicate specimens from the same patient were excluded from the study. Ethical exemption was obtained from Ethical Review Committee of The Aga Khan University Hospital, Pakistan (3303-Pat-ERC-14).

For blood culture, clinical microbiology laboratory uses an automated system since 1998. Initially, BACTEC 960 automated system was in place, which was replaced by BACT Alert system in 2016. Routine identification of microbial isolates was done using conventional methods. Once the blood culture grew gram negative, non-lactose fermenting and oxidase positive colonies, further biochemical tests for identification of BCC were performed. As per standard operating procedure, BCC was identified as a motile Gram-negative rod, appearing as oxidiser on oxidative /fermentation media, with an alkaline/ alkaline reaction on triple sugar iron agar and negative reaction to sulphide and indole and citrate agars appearing resistant to polymyxin B on disk susceptibility testing.

This was performed using Kirby Bauer disc diffusion method according to the Clinical and Laboratory Standards Institute (CLSI) guidelines for BCC. [13]

Further, antimicrobial resistance pattern of BCC was determined against antimicrobial agents including trimethoprim-sulfamethoxazole (SXT), levofloxacin (LEV), ceftazidime (CAZ), meropenem (MEM), ciprofloxacin (CIP), and minocycline (MINO), interpreted as per the CLSI guidelines.[12]

Data was entered and analysed using the statistical software SPSS version 19.0. Frequencies with percentages were computed to determine the positive trend for laboratory confirmed BCC cases at AKUH, the age group most affected by BCC infection and the susceptibility pattern of the BCC culture positive specimens.

RESULTS

During 14 years of study period (2008-2021), a total of 5411 blood culture specimens showed growth of BCC as shown in Figure-I. Amongst these BCC positive cultures, 3410/ 5411 (63%) specimens belonged to male gender. Healthcare location data showed that only 624(11.5%) positive cultures belonged to AKUH hospitalized patients while remaining 4787 (88.5%) blood culture were submitted from other healthcare settings. Figure-II shows allocation of BCC cepacia bacteremia in different ages of the study subjects; neonates being the predominant group each year.

We observed highest resistance in BCC strains against levofloxacin, isolated from both in-patients and out-patients (around 37%). Meropenem resistance was also 37% in in-patients isolates while 25% in out-patient isolates (Figure-III).

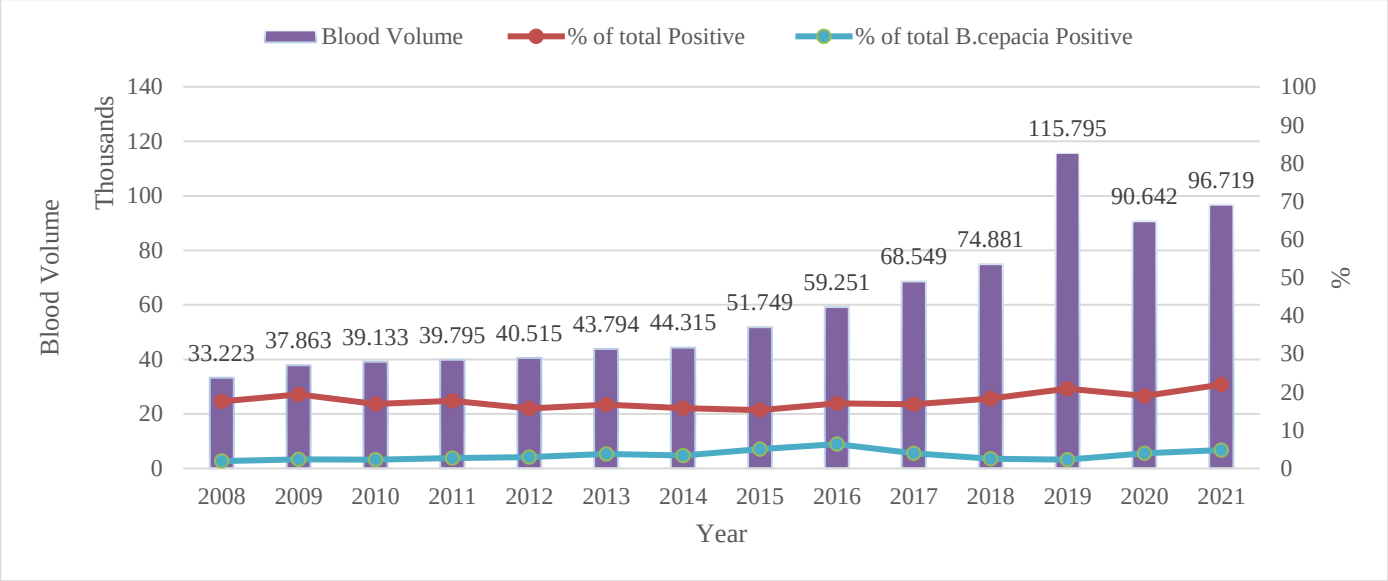

Figure-I: Blood culture bottles submitted on yearly basis (2008-2021), along with *B. cepacia positivity* rate in percentage.

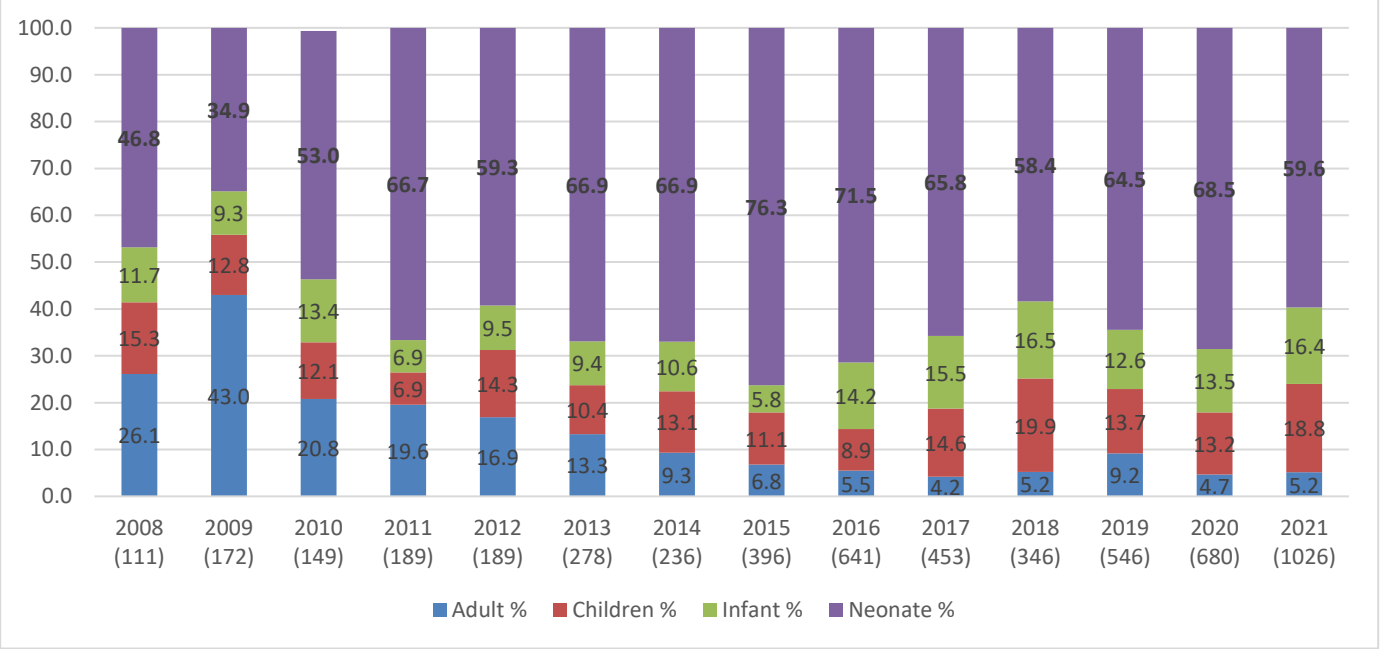

Figure-II: Distribution of *B. cepacia* in different age groups over the years.

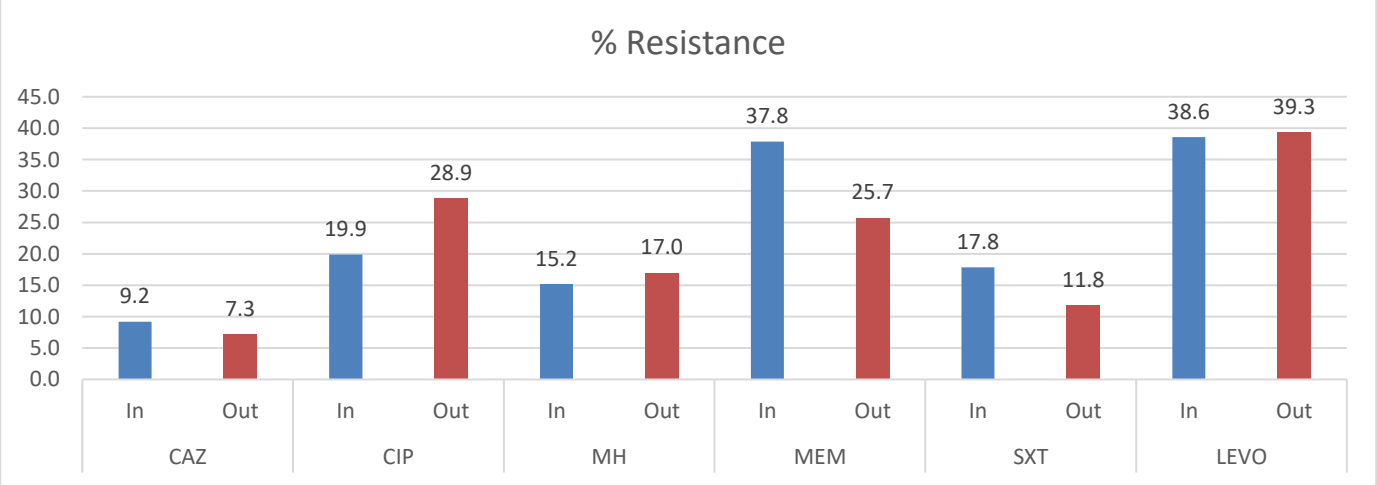

Figure-III: Percentage of antimicrobial resistance amongst *B. cepacia* isolated.

DISCUSSION

This study revealed that during years 2008-2021, BCC strains contributed to a significant proportion of bacteraemia isolates, especially in neonatal age group. In developing countries, septicaemia is known to be one of the important cause of deaths in neonates,[18] which might be due to weakened immune responses, or due to hospital acquired infections in neonatal ICUs. While other studies show varying profiles,[19, 20] neonates were the most affected group in which BCC septicaemia was observed. Since AKUH laboratory has more than 200 collection points across the country, samples from several other hospitals are sent here for cultures. Hence, the neonatal outpatient population may very likely be from neonatal units in other hospitals. It is an unfortunate limitation that we could not confirm whether outside referrals were hospital acquired infections or otherwise.

Considering the predominance of BCC isolated in neonatal blood cultures, it is important to explore infection control practices in neonatal intensive care units. Several outbreaks have been reported, not only from Pakistan[14-17] but also from other countries[,21-23] indicating that the organism has a propensity to inhabit and infect this vulnerable niche. Strict terminal cleaning protocol should be employed once the organism has been isolated from a patient to prevent its colonization and spread.

The higher resistance to meropenem in hospitalized patients might be due to increased utilization of meropenem in this population, and vice versa for meropenem. Other antibiotics like ceftazidime, cotrimoxazole and minocycline showed no difference in % of resistance amongst both groups. BCC is one of those bacteria that are known to be inherently resistant to various antimicrobial agents and poses great difficulty to clinicians to manage patients infected with it.[11] As per the CLSI 2016 guidelines,[13] the drugs recommended to be tested against BCC are levofloxacin, cotrimoxazole, ceftazidime, meropenem and minocycline. Levofloxacin has shown to be highly efficacious against BCC isolates,[24] due to its bactericidal activity by inhibiting DNA gyrase and topoisomerase IV [25]. Previous studies have shown that BCC is susceptible to meropenem irrespective of species status. Clinical studies have also reported that patients infected with BCC were successfully using ceftazidime and meropenem.[10] In addition, for respiratory infections, nebulization with drugs such as meropenem or tobramycin are also shown to be effective. In this study resistance against both levofloxacin and meropenem was found high making empirical choice very difficult. Interestingly, resistance to levofloxacin was higher than ciprofloxacin in the study, attributable to possible divergence in selective pressure or prescribing practices. Although the organism may appear susceptible to trimethoprim-sulfamethoxazole and ceftazidime in-vitro, but BCC develops quickly under antimicrobial pressure.[27]

Latest guidelines from the CLSI [28] recommend susceptibility testing to not be performed against *B. cepacia* by any method whatsoever, however, laboratories may report MICs without providing interpretation, with this disclaimer: “Antimicrobial susceptibility is not routinely performed for B. cepacia complex due to the lack of accurate test methods” and that although “broth microdilution is the only reproducible method, correlation of MIC values with clinical outcomes is not known”. Since our study does not include clinical features, we cannot comment on this guideline revision based on clinical correlation

CONCLUSIONS

Higher resistance rates of *Burkholderia cepacia* complex to certain antibiotics in different patient populations was observed which corresponds with the settings in which these antibiotics are used, and emphasizes the need for use of continuous surveillance of *Burkholderia cepacia* complex antibacterial resistance using appropriate testing to monitor the spread of resistance. In addition, there is also a risk of a spread of resistant bugs from the affected group to community. Hence it is important to improve infection control and antibiotic prescription practices in all type of health care settings, especially in tertiary care cents where complicated cases are handled. This study highlights the need to refine approaches for testing, controlling antimicrobial prescription and infection control practices to combat the growing resistance in *Burkholderia cepacia* complex isolates.

CONFLICT OF INTEREST

None

GRANT SUPPORT & FINANCIAL DISCLOSURE

Declared none

AUTHOR CONTRIBUTION

Seema Irfan: Substantial contribution to study design, acquisition of data, analysis and interpretation of data, manuscript drafting, final approval, accountable for all aspects of publication.

Fizza Farooqui: Substantial contribution to analysis and interpretation of data, critical review, final approval, accountable for all aspects of publication.

Kiran Iqbal: Substantial contribution to acquisition of data, manuscript drafting, final approval, accountable for all aspects of publication.

Afia Zafar: Substantial contribution to study design, critical review, final approval, accountable for all aspects of publication.

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