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# Burkholderia Cepacia: An Emerging Superbug in Intensive Care Unit Settings of Tertiary Care Hospitals in Pakistan

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## ABSTRACT

***Objective:*** To determine the frequency, risk factors, and antibiotic susceptibility pattern *of Burkholderia cepacia* isolates from clinical specimens in a Pakistani tertiary care hospital.

***Study Design:*** Cross-sectional Study

***Place and Duration of Study:*** Department of Microbiology, Armed Forces Institute of Pathology, Rawalpindi Pakistan, from Jul 2017 to Jun 2021.

***Methodology:*** The *Burkholderia cepacia* strains were isolated from clinical samples by routine microbiological methods. In our laboratory, the identification and antimicrobial susceptibility testing of the isolate were made by API 20NE and VITEK-2 Automated Microbiology Analyzer.

***Results:*** Four hundred and nineteen (419) str5-ains of *Burkholderia cepacia* were isolated during the study period. Among them, 277(66.1%) and 57(13.6%) isolates were from blood cultures and lower respiratory tracts, respectively. The antibiotic-resistant rates of the isolates of *Minocycline, Cotrimoxazole, Levofloxacin, Meropenem,* and *Ceftazidime* were 13(3.1%), 26(6.2%), 49(11.6%), 74(17.6%) and 118(28.16%) respectively.

***Conclusion:*** We observed a gradual increase in the frequency of isolation. A surge in antimicrobial resistance was also seen during the study period underscoring the need for rigorous implementation of antimicrobial stewardship programs and infection control practices.

**Keywords**: Antimicrobial susceptibility, Bloodstream infections, *Burkholderia cepacia* complex (BCC), Minocycline, Multidrug resistance.

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## INTRODUCTION

*Burkholderia cepacia* comprises closely related species known as *the Burkholderia cepacia* complex. It is an environmental saprophyte found in soil, water and agricultural products. The bug, once considered a phytopathogen, is increasingly seen as an opportunistic nosocomial pathogen in hospital settings.[1,2]

The emergence of *Burkholderia cepacia* as a nosocomial pathogen, particularly in ICU settings, is attributed to several unique features of this microorganism. These include innate and acquired resistance to numerous antibiotics leading to a limited repertoire of antibiotics to be used, florid survival and growth in an aqueous hospital environment. In addition, person-to-person transmission and nosocomial contact through medical devices and contaminated disinfectants also play a key role in making it a dreadful pathogen. Moreover, host factors like immunocompromising states, pre-existing lung diseases, prolonged hospital stay, and broad spectrum antibiotics and hardware play a notable role in making the situation even more alarming.[3,4]

*Burkholderia cepacia* is the etiological agent of several hospital-acquired infections, including types of pneumonia, particularly in patients with pre-existing lung diseases, e.g. cystic fibrosis, bacteremia, urinary tract infections, infections of the musculoskeletal system, skin and soft tissue infections and rarely shunt related meningitis. The morbidity and mortality associated with this pathogen are quite high, ranging from 1.2%–to 53%, reiterating the dire need for its survei-llance and infection control measures.[5,6] Since there is a paucity of data from our part of the world regarding the frequency and antimicrobial susceptibility profile of *Burkholderia cepacia*, the rationale of this study was to assist our clinical colleagues in selecting optimal Antimicrobial therapy in our setups whenever this pathogen is encountered in various clinical samples of patients.

## METHODOLOGY

We conducted a cross-sectional study for the surveillance of this relatively unheard pathogen at the Department of Microbiology, Armed Forces Institute

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of Pathology, Rawalpindi Pakistan, from July 2017 to June 2021. Permission was taken from the Institutional Ethical and Review Board (READ-IRB/21/480). Non-probability, consecutive sampling was carried out. Relevant clinical information was retrieved from the Laboratory information management system of the Department of Microbiology for all isolates of *B cepacia* isolated from different clinical specimens.

**Inclusion Criteria:** Samples from the Inpatient and Outpatients Departments (including various types of respiratory cultures, blood cultures, sterile fluids, pus and tissue specimens) of the patients of all ages group and either gender were included in the study.

**Exclusion Criteria:** Repeat samples of the same patients were excluded from the study.

Standard microbiological techniques were employed to isolate the organism from clinical samples.[7] The samples were inoculated on routine bacteriological media. Necessary tests like catalase, oxidase and motility were performed. The colony morphology was also noted. API 20NE was employed for species-level identification of the isolate.

Further confirmation was done by the automated microbiology analyzer Vitek 2 (version 8.02). Antibiotic susceptibility tests were performed according to modified Kirby Bauer disc diffusion methodology using interpretative criteria given in CLSI current for the particular year.[8] For two antimicrobials, i.e., Chloramphenicol and Levofloxacin, CLSI recommends Minimum Inhibitory concentrations. For this purpose, Vitek 2 was utilized, which gives MICS using Broth microdilution.

Data were analyzed in MS Excel 2016 software. Mean±SD were calculated for the continuous variable. In addition, frequency and percentage were calculated for categorical variables.

## RESULTS

*B. cepacia* was isolated from clinical samples of 419 patients. There was no clustering of *B. cepacia* infections in time and space during the study period. For ease of assimilation, the clinical samples were split into half-yearly brackets. Initially, in the second half of 2017, only 19 isolates were detected. In the next years, we observed a gradual increase in isolates from January 2018 to December 2020. However, a sharply increased trend of isolating this nosocomial pathogen was observed in 2021, being a record high of 137 isolates, shown in Figure-1.

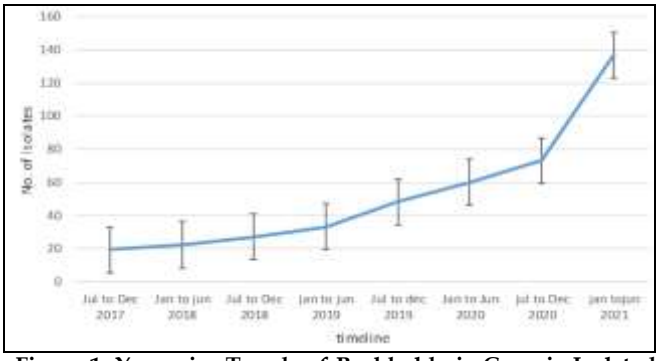


**Figure-1: Year wise Trends of Burkholderia Cepacia Isolated from various Clinical Specimens**

In our setup, *B.cepacia* was most commonly isolated from medical ICUs 198 (47.2%) followed by surgical ICU 110(26.25%). The number of Isolates from Neonatal and Pediatric ICUs was almost the same being 25(5.9%) and 26(6.2%), res-pectively. The remaining 60(14.36%) were isolated from wards like Orthopedic wards, ENT, Urology and Oncology wards shown in the Table-I.

**Table–I: Burkholderia Cepacia Isolates from Different Units of the Hospital (n=419)**

| Hospital Units | Frequency (%) |
|---|---|
| Medical ICU | 198(47.20) |
| Surgical ICU | 110(26.25) |
| Neonatal Intensive Care Unit | 25(5.90) |
| Pediatric Intensive Care Unit | 26(6.20) |
| Others | 60(14.36) |

The age range in this study was from newborn to 90 years, with a mean age of 47.10±3.50 years. Out of the 419, *B.cepacia* isolates majority of isolates, 272 (64.9%), were recovered from specimens of males and 147(35.08%) from specimens deposited by females. The ratio of males to females was observed to be 1.85:1. An investigation into the predisposing causes was initiated, whereby it became apparent that prior antibiotic use 381(91%) was the main risk factor for the colonization/ infection caused by this bacteria. This was followed by external hardware, particularly Mechanical ventilatory tubes 289(69%) and the CVP line. The presence of a urinary catheter cannot be undermined. Both solid organ and haematopoietic malignancy were also notifiable predisposing factors (Table-II).

We found that 272 *B.cepacia* isolates were yielded from Blood cultures and five isolates from Bone marrow aspirate cultures. Next in line were respiratory cultures (including endobronchial washings, bronchioalveolar lavage, sputum and nondirected

bronchial lavage), being 57. The least number of only ten isolates were seen in other sterile body fluids like CVP line fluid, synovial fluid, and pericardial and ascitic fluids shown in Figure-2.

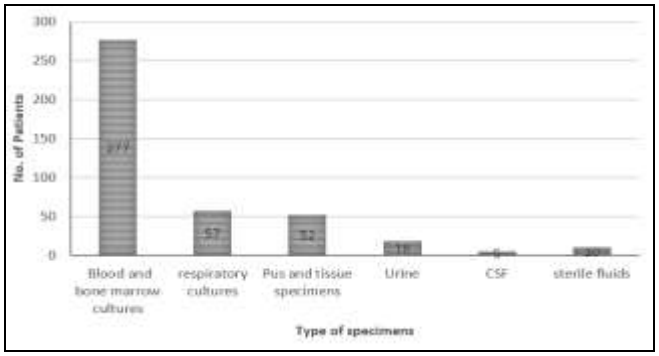


**Figure-2: Burkholderia Cepacia Isolates from Different Patient Specimens**

Our study found antimicro-bial resistance rates among *B. cepacia* strains to be high. Minocycline, Cotrimoxazole and Chloramphenicol were the most active antimicrobial agents against *B. cepacia* isolates. The percentage resistance of Ceftazi-dime, Meropenem and Levoflo-xacin was high greater than 10% as shown in Table-III.

**Table–II: Burkholderia Cepacia and Patient Characteristics (n=419)**

| Characteristic | n(%) |
|---|---|
| **Gender** | |
| Male | 272(64.9) |
| Female | 147(35.1) |
| Age (Mean±SD) (years) | 47.10±3.50 |
| **Risk factors n(%) of patients** | |
| Mechanical ventilation | 289(69.0) |
| Other hardware (urinary catheter ,CVC) | 368(88.0) |
| Antibiotic use | 381(91.0) |
| Malignancy | 50(12.0) |
| Diabetes mellitus | 150(36.0) |

**Table–III: Antimicrobial Resistance Rates of B.Cepacia Isolates (n=419)**

| Antibiotics | Resistance n (%) |
|---|---|
| Cotrimoxazole | 26(6.20) |
| Ceftazidime | 118(28.16) |
| Meropenem | 74(17.60) |
| Minocycline | 13(3.10) |
| Levofloxacin | 49(11.60) |
| Chloramphenicol | 30(7.150) |

## DISCUSSION

*B.cepacia* is Non-fermenting, Late oxidase positive Gram Negative rod. It is a common cause of hospital-acquired infections in debilitated and immunocompromised populations, particularly in ICU settings, and other Non-fermenters, namely *Pseudomonas aeruginosa*, *Acinetobacter baumanii* and *Stenotrophomonas maltophila*.[8,9,10] It rarely causes infection in healthy and immunocompetent individuals. *Burkholderia cepacia* is commonly isolated from the hospital environment and equipment such as ventilator circuits, Nebulizers, linen, and other apparatus.[11,12] It also colonizes the skin of healthcare workers. *Burkholderia cepacia* shows intrinsic resistance to most of the β-lactam agents, aminoglycosides, macrolides and polymyxins. Due to high intrinsic resistance encountered in the clinical laboratory, this infection can prove fatal.[13,14]

During the study period, 419 Burkholderia *cepacia* isolates were retrieved from clinical samples of the patients. Out of which 272 were male, and 147 were female. The male-to-female ratio is 1.85:1. This gender distribution was compatible with Keating *et al*. who reported similar findings.[9] In the present study prevalence of *Burkholderia cepacia* was studied according to the age of the patient. The highest prevalence was noted in adults aged between 40 to 60 years which was 64%, and the least in neonates, 3%.[10]

The study showed a timeline in which an increasing trend of Isolation of *B.cepacia* was seen. This establishes the significance of this isolate in our setup. One plausible reason for the sharp rise in cases may be the high proportion of superadded infections in patients suffering from COVID-19, particularly in the year 2021. Literature review shows that nosocomial infections of *B. cepacia* are mainly limited to outbreaks. However, here we see a steady increase in isolation of this bacterium mainly because of our better diagnostic facilities and gaps in infection control practices.[15]

The spectrum of *B.cepacia* infections among patients of various units of this institute was assessed in this study. A high percentage of *B.cepacia* were isolated from specimens of patients admitted in medical intensive care units and surgical intensive care units, followed by Paediatric intensive care units, neonatal intensive care units, and wards like medical orthopaedic and pediatric wards. This observation is quite homologous to other studies undertaken in various regions across the biosphere.[5,15]

BCC causes a spectrum of clinical infections that include bacteremia, respiratory tract infections, urinary tract infections, joint infections, and abdominal infections.[16] The specimen from where the isolate was most frequently identified as blood cultures. This was follo-

wed by respiratory, pus, and tissue specimens and hence indicated to cause infections at these relevant sites. A study published in the Annals of Tropical Medicine and Health showed that the prevalence of *Burkholderia cepacia* was highest from blood cultures.[17] A study in China showed that respiratory specimens were on top.[18]

Our study demonstrated that Minocycline was the least resistant antimicrobial agent, followed by Cotrimoxazole 6.2%, Chloramphenicol 7.15% and Levofloxacin 11%. These antibiotics, either alone or in combination with other antimicrobial agents, may be considered appropriate therapeutic options for *Burkholderia Cepacia* infections, depending on the invitro susceptibility patterns and clinical results. Betalactam agents, including Ceftazidime and Meropenem, showed higher resistance owing to the high utilization of these agents in our setup resulting in the selection of resistant bugs. This was contrary to a study by Patra *et al*. in 2014 in which susceptibility to Meropenem was 100%, followed by Ceftazidime-sulbactam and Pipera-cillin Tazobactam.[17] Another study in Bangladesh showed 100% sensitivity to Meropenem, and 93% of isolates were resistant or intermediate to levofloxacin.[19] The results from SENTRY Antimicrobial surveillance program showed greater than 90% susceptibility to Minocycline, similar to our results in which Minocycline is considered the most effective antibiotic.[20]

However, the current clinical information is not adequate, and further studies are necessary to determine the in vitro efficacy of these antimicrobial agents for Burkholderia cepacia infections. These deviations in antibiotic susceptibility results are possibly due to the varying antibiotic dogmas followed by the hospital. These results also highlight the necessity of correct identification and antibiotic susceptibility testing of *Burkholderia cepacia* to devise appropriate therapeutic choices.

## LIMITATIONS OF STUDY

The non-availability of molecular techniques like PCR and NGS in our study was the limitation in determining subspecies coming under the umbrella of the B.cepacia complex. Antibiotic escalations and deescalations were done according to our culture and sensitivity report, but we failed to follow up on the outcome of the patient after our interven-tions. Furthermore, the sensitivity of this isolate was not checked for some new antibiotics, not like Ceftazidime, Avibactam.

## CONCLUSION

The current study strengthens the importance of *B cepacia* as an opportunistic nosocomial pathogen in Pakistan. Therefore, diagnostic laboratories must be well-equipped for isolation, identification and antibiotic sensitivity testing of these strains to help physicians decide on optimal antimicrobial therapy. This will be essential in reducing morbidity and mortality attributable to this superbug.

**Conflict of Intrest:** None.

**Author's Contribution**

Following authors have made substantial contributions to the manuscript as under:

RI & AA: Data acquisition, data analysis, critical review, drafting the manuscript, critical review, approval of the final version to be published.

IAM & WH: Conception, Study design, drafting the manuscript, approval of the final version to be published.

MS & MA: Critical review, data interpretation, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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