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Original Article

Microbiology Section

Burkholderia cepacia from an Unidentified Organism to an Emerging Pathogen in a Tertiary Care Hospital- A Retrospective Study

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ABSTRACT

Introduction: *Burkholderia* is an important opportunistic pathogen in hospitalised and immunocompromised patients. It is responsible for approximately 0.6% of all Ventilator Associated Pneumonia (VAP). *Burkholderia cepacia (B. cepacia)* is a resilient organism, capable of survival in environments devoid of significant nutritional resources. Authors have come across many cases of *B.cepacia* in hospital for the last six years.

Aim: To know the prevalence and microbiological profile of *Burkholderia* infection in tertiary care hospital, Srinagar, India.

Materials and Methods: The present retrospective study was carried out in the Department of Microbiology, Sher-i-Kashmir Institute of Medical Sciences, Srinagar, Jammu and Kashmir, India, from January 2013 to October 2018. The records of all patients diagnosed with *B.cepacia* in Intensive Care Unit (ICU), wards, and Outpatient Department (OPD) were reviewed. Identification was done by Vitek 2. Descriptive analysis was done and data was presented as percentages.

Results: The number of cases showed a steady rise from 2013 through 2016 and the peak number of cases occurred in the year 2016. Then, again the numbers started to decline. Surgical ICU was the most common location (n=490) where the cases were detected. Most of the isolates were sensitive to cotrimoxazole, ceftazidime, tigecycline and levofloxacin and moderately sensitive to minocycline and meropenem.

Conclusion: *Burkholderia* is no longer restricted to patients with Cystic Fibrosis (CF) and can affect patients in ICU setting and that the mortality from the infection remains high in our part of the world. Further studies are needed to be carried out to address this issue.

Keywords: Emergence, Nosocomial infection, Sepsis, Surveillance, Ventilator associated pneumonia

INTRODUCTION

Despite tremendous advances in our understanding of microbial pathogenesis over the last 50 years, combating bacterial infections continues to be an important part of the medical efforts in hospital and community settings. Improvements in the treatment of genetic diseases, cancer and organ transplantation have resulted in an increased incidence of immunosuppression and the rise of opportunistic infections. In particular, non fermenting gram negative bacteria pose a significant problem in the clinical environment, as they are a common cause of nosocomial infections and are resistant to many antibiotics [1]. The common opportunistic pathogens in this group are *Pseudomonas, Acinetobacter, Stenotrophomonas, Burkholderia*, and *Ralstonia* spp. In hospitals, these organisms grow in humidifiers, mattresses, ventilators, and disinfectant solutions and can form biofilms [2].

B. cepacia is not a single organism but rather a collection of related species collectively referred to as the *B. cepacia* complex (Bcc). Bcc and non Bcc species of the *Burkholderia* genus are diverse and can adapt to varying environmental conditions including nutrient scarcity, antibiotics, antimicrobial peptides and toxic substances [3]. *Burkholderia cepacia* is a gram negative, aerobic, non fermenting bacillus usually found in soil and moist environments. This reflects its innate ability to survive and grow in water sources with minimal nutrition. This organism particularly affects the lungs in patients with Cystic Fibrosis (CF) and is regarded as an important opportunistic pathogen in hospitalised and immunocompromised patients. It is responsible for approximately 0.6% of all Ventilator Associated Pneumonia (VAP) [3]. *B. cepacia* is a resilient organism, able to survive in environments devoid of significant nutritional resources. It can grow in aqueous environments and on surfaces commonly found in hospitals, such as polyvinyl chloride, a material frequently used in respiratory therapy equipment [4]. The organism is not only resistant to many antibiotics but also to disinfectants. This makes their survival easy in restricted areas like ICU and makes their management difficult. Outbreaks of *B. cepacia* infections have been associated with contaminated respiratory therapy equipment, solutions, and medications and with unsafe infection control practices [5]. Identification of non fermenters remains problematic particularly in laboratories using manual identification. However, with the availability of automated systems like Vitek, the identification of non fermenters has improved to a great extent [6,7]. The vitek 2 was installed in 2012 in our department and since then an increased number of *B. cepacia* have been reported in our hospital for the last six years. Therefore, the study presented the experience with the identification, prevalence, and microbiological profile of this infection in the hospital as this infection has significant mortality and no such study has been published from this region so far.

MATERIALS AND METHODS

The present retrospective study was conducted in the Department of Microbiology, Sher-i-Kashmir Institute of Medical Sciences, Srinagar Jammu and Kashmir, India, from January 2013 to October 2018 and the data was analysed in October 2019. The records of all patients diagnosed with *B. cepacia* in ICU, wards, and OPD were reviewed after approval from the Institute Ethial Committee (IEC) under the protocol no IEC/SKIMS Protocol # RP 180/2021.

Microbiological Analysis

Blood culture: Blood culture samples were collected in blood culture bottles BacT/ALERT (bioMérieux). The samples were incubated in the BacT/ALERT system (bioMérieux) and monitored periodically. Bottles having positive signals were retrieved from the system, gram-stained and cultured on blood agar and MacConkey agar plates. On blood agar, the microorganism produced opaque, glistening colonies, which were non pigmented initially, later developed yellow pigmentation, and were non lactose fermenting colonies on MacConkey agar. Colonies of the organisms formed on the agar plates were identified

and Antimicrobial Susceptibility Testing (AST) was done by the Vitek-2 system. A standard inoculum was prepared from different colonies formed on agar medium, and the appropriate Vitek-2 cards were inoculated following the manufacturers' recommendation.

Surveillance culture: Surgical Intensive Care Unit (SICU) surveillance samples were obtained with swabs and sent to the hospital's microbiology laboratory. Samples were taken from suction apparatus, ventilator tubings, Ambu bags (Ambu, Ballerup, Denmark), injection preparation trollies, amikacin injection vials, taps, bed railings, Cheatle forceps, and from saline for injection preparations. The swabs were on blood agar plates and incubated at 36°C overnight under aerobic environment. The results were read the following day, and the colonies were identified with gram staining and biochemical tests. The isolates were confirmed using the Vitek-2 system (BioMérieux). The antimicrobial susceptibility of the organisms was performed by both the Kirby-Bauer disc diffusion method and the VITEK 2 AST card [8]. Surveillance was carried out in SICU and authors isolated *B. cepacia* from a particular mouth wash that was being sold in the local market. Authors purchased fresh samples of the same mouthwash from the market and isolated *B. cepacia* from the fresh samples using the Vitek 2 system thus, establishing a link between the source and the outbreak.

STATISTICAL ANALYSIS

The results were presented as descriptive statistics in terms of relative frequency.

RESULTS

A total of 918 isolates were detected within the time period. After isolation of *B. cepacia* in the first case in 2012, the authors became conscious about the presence of species, so the present study was conducted and the number of cases isolated in subsequent years increased. The maximum number of cases were isolated in 2016 (330) followed by 2017 (264), 2018 (174), and least were in 2015 (110) as shown in [Table/Fig-1]. The maximum number of cases in each year were seen in SICU (490, 53.4%) followed by Inpatient Department (IPD) (346/918, 37.7%). The month wise distribution of cases has shown in [Table/Fig-2] where maximum cases were seen in the month of March (107, 11.6%). The most common locations from where the organism was isolated in the hospital were, accident emergency, nephrology ward, gastroenterology ward in the initial years of the study and later surgical ICU was the predominant place from where the organism was isolated [Table/Fig-3]. The organisms were sensitive to cotrimoxazole (91.91%), ceftazidime (85.71%), levofloxacin (84.48%), and tigecycline (82.94%). The organisms showed intermediate sensitivity to meropenem (29.47%) and minocycline (42.86%). A 13.46% of organisms were resistant to meropenem [Table/Fig-4]. Samples that were taken from multiple sources within the hospital during surveillance that did not grow any species. However, *B. cepacia* was grown from a mouth wash (Hexafresh) collected from bed side and from the fresh one purchased from the market [Table/Fig-5].

Year	Isolates	SICU[a]	MICU[b]	PICU[c]	NICU[d]	IPD	OPD	Others
2013	1	0	0	0	0	1	0	0
2014	39	3	2	0	0	33	0	1
2015	110	10	0	1	1	87	5	6
2016	330	158	8	0	3	137	19	5
2017	264	190	0	0	0	51	4	19
2018	174	129	0	0	1	37	5	2
Total	918	490	10	1	5	346	33	33

[Table/Fig-1]: Year-wise distribution of isolates of *B. cepacia* (n=918).
[a]Surgical ICU; [b]Medical ICU; [c]Paediatric ICU; [d]Neonatal ICU; Others: Samples received from other hospitals; IPD: Inpatient department; OPD: Outpatient department

Years	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
2013	0	0	0	0	0	1	0	0	0	0	0	0
2014	0	1	3	1	0	0	8	3	5	6	7	5
2015	4	5	12	10	8	6	7	8	9	17	13	11
2016	21	20	29	24	31	32	34	27	24	30	33	25
2017	34	26	42	28	39	10	11	9	20	12	17	16
2018	18	16	21	16	20	18	14	17	13	10	6	5
Total	77	68	107	79	98	67	74	64	71	75	76	62

[Table/Fig-2]: Month-wise distribution of isolates of *B. cepacia*.

Years	Most common location (Ward No.)	No. of cases detected	Percentage (%)
2013 (1)	A/E[a]	1	100
2014 (39)	4A	15	38.46
2015 (110)	3A	24	21.8
2016 (330)	SICU[b]	151	45.7
2017 (264)	SICU[b]	186	70.5
2018 (174)	SICU[b]	129	74.2

[Table/Fig-3]: Most common site of isolates of *B. cepacia* as per location in hospital.
[a]A/E: Accident and emergency; [b]SICU: Surgical intensive care unit 4A (Nephrology ward), 3A (Gastroenterology ward)

Antibiotics	Total isolates tested	Sensitive	Intermediate sensitive	Resistant	Sensitivity	Intermediate sensitivity	Resistant
Ceftazidime	511	438	31	42	85.71%	6.07%	8.21%
Levofloxacin	509	430	13	66	84.48%	2.55%	12.97%
Meropenem	587	335	173	79	57.07%	29.47%	13.46%
Minocycline	511	284	219	8	55.58%	42.86%	1.57%
Co-trimoxazole	643	591	0	52	91.91%	0.00%	8.09%
Tigecycline	645	535	77	33	82.94%	11.94%	5.12%

[Table/Fig-4]: Antibiotic sensitivity of *B. cepacia* isolates.
The sensitivity was done by Vitek-2 which is an automated system for doing sensitivity. All the samples were not tested for all the antibiotics. However, all samples were tested for more than one antibiotics to see the sensitivity pattern

Swab taken from	Organism grown	Swab taken from	Organism grown	Swab taken from	Organism grown
DNS bottle with KCL 40 mg	Sterile	Mouth wash B	Sterile	NS for injection from SICU[a]	Sterile
Povidone Iodine 10%	Sterile	Monitor screen	*Micrococcus*	Neuro ICU Humidified water	CONS
Heparinised saline	Sterile	Tracheostomy site	*Acinetobacter baumannii*	NS 500 mL fresh	Sterile
Transducer	CONS	CVC[b] outer lumen	Sterile	Water supply from SICU[a]	Sterile
Heparinised saline from CVC[b]	Sterile	Hand swab from patient	CONS	Water supply from MICU[c]	Sterile
Mouthwash A	Sterile	Patient's feed	Spore Bearers	Tap water Surgical emergency	Sterile
Bed rails	*Pseudomonas aeruginosa*	NS Bedside	Sterile	Oxygen Humidifier	*Pseudomonas stutzeri*
Water from purifier in ward	Sterile	NS for injection	*Sphingomonas paucimobilis*	NS 500 mL for injection	Sterile
Noradrenalie injection	Sterile	Cidex of Neurosurgery Operation table	Sterile	2% inj Lignocane 30 mL bottle	Sterile
Listerine mouthwash	Sterile	Mouth wash B	Sterile	2% Lignocane jelly	Spore Bearers
NS of lab	Sterile	Syringe on side table	*Acinetobacter baumannii*	Syringe with saline	Sterile

Distilled water of lab	*E.coli*	Femoral site of patient	Sterile	Tap water from Emergency OT	*Sphingomonas paucimobilis*
Water for flushing	Sterile	Water from SICU[a] Washrooms	*Micrococcus*	Water Humidifier resusication trolley	*Pseudomonas aeruginosa*
Hexafresh (Mouthwash) from patient	*B. cepacia*	Fresh Hexafresh (Mouthwash) from market	*B. cepacia*	---	---

[Table/Fig-5]: Organisms grown from swabs taken from various sites during surveillance.
[a]Surgical intensive care unit; [b]Central venous catheter; [c]Medical Intensive care unit; ICU: Intensive care unit; CONS: Coagulase negative *Staphylococcus*; OT: Operation theatre; DNS: Dextrose normal saline; KCL: Potassium chloride; NS: Normal saline

DISCUSSION

The Bcc organisms are opportunistic pathogens that can cause severe infection in immunocompromised patients, especially those with CF [9]. In such patients, Bcc infection causes "Cepacia syndrome", usually characterised by sepsis, necrotising pneumonia, and an overall bad prognosis. Although many species from this group are isolated from the lungs of CF patients, *B. cenocepacia* and *B. multivorans* appear to cause the most serious infections in these patients and account for about 85% of all Bcc infections [10]. The importance of Bcc infections in CF has been recognised for over 25 years now. With more patients of CF surviving infection with *B. cepacia* may even increase further. Numerous studies have documented the importance of *B. cepacia* is a life-threatening pathogen in patients with CF and to a lesser extent in other immunocompromised conditions and diseases [1,2,11]. It is well documented that the *B. cepacia* group may spread rapidly among patients with CF, both within and outside the hospital [12]. Lung infections with *B. cepacia* in patients with CF may end in progressive, invasive, and fatal septicaemia [12]. However, few studies have documented the occurrence of fatal blood infections with *B. cepacia* in immunocompetent patients [1,10].

This study describes the emergence of blood infections with the Bcc group in hospitalised patients with certain underlying diseases aside from CF. In the present study, authors encountered a surge in the isolation of the organism from the year 2013 to 2016 with only one patient in 2013 to 330 isolates grown in 2016. Upto 2012, we were identifying organisms by manual tests and most of the non fermenters like *Burkholderia* may have missed. After the installation of Vitek-2, the identification was done using the same and most organisms were identified from 2013 to 2017. Afterwards, the number of isolates started declining although it continues to be at 174 isolates in 2018. The reason for this decline was that the infection control measures were taken and the identification of the source was done. A thorough investigation was carried out and samples were taken from multiple sources within the hospital to look for the source of the infection but could not find the source of infection.

Subsequently, surveillance was conducted in the Neurosurgery operation theatre. Swabs were taken from the cidex tray, floor, operating table, and scrub station. The organisms isolated were *E coli*, Coagulase negative *Staphylococcus* (CoNS), and aerobic spore bearers. Afterwards, another surveillance was conducted in SICU, and samples were taken from injection trollies, ventilator beds, HME filters AC vent, drug ampules the organisms have grown were Methicillin-resistant coagulase-negative staphylococci (MRCoNS), Multidrug resistant (MDR) bacteria *Klebsiella pneumonia*, MDR *E coli*, MDR *Acinetobacter baumannii* and spore bearers, *Serratia* species. Bilgin H et al., reported the isolation of similar organisms from ICU in a tertiary care hospital in Turkey [13]. Russotto V et al., also isolated similar organisms from ICU in their hospital [14]. In August 2018, Centers for Disease Control and Prevention (CDC) team also carried out surveillance in our hospital and took samples from various places like DNS bottles, Transducers, bed rails, povidone-iodine, mouthwashes, etc, and isolated different types of organisms like *Pseudomonas, Acinetobacter, Sphingomonas, Chryseobacterium indologenes,* and *Pseudomonas stuzeri*. etc., but again were unable to find the source of infection. One interesting finding was that authors isolated *Chryseobacterium indologenes* from the towel. The organism is similar to *B. cepacia* and Vitek sometimes misidentifies *B. cepacia* as *Chryseobacterium indologenes*. Further identification to differentiate *B. cepacia* and *Chryseobacterium indologenes* was not carried out.

The isolation of *B. cepacia* from the fresh samples of mouthwash purchased from the market and confirmed using the Vitek 2 system thus, established a link between the source and the outbreak. The observations are similar to Wong SCY et al., who isolated *B. cepacia* from mouthwashes from the outside hospital in Hong Kong China [15]. Bilgin H et al., also isolated *B. cepacia* from 17 out of 17 samples of mouthwash from a specific batch in their hospital [13]. The month wise distribution of cases shows that there was an increase in the number of cases initially which peaked around March 2017 (42 isolates) and then steadily decreased possibly pointing to a potential source of infection during that period. The SICU was the most common location where the organism was grown. The possible reason was the decreased immunity of these patients and the spread of infection from one patient to another because of the proximity in an ICU and relocation of ICU. The reason was that the relocated ICU was not set up as per standard guidelines. This ICU was not having a proper washing area, had inadequate staff, and was congested with patients. Bcc has a singular and challenging antimicrobial profile. They are resistant to multiple antibiotics, especially to the commonly prescribed like aminoglycosides, second generation cephalosporins, and polymyxin [16]. Different resistance patterns are reported within the different outbreaks that have occurred worldwide [9,17,18].

Fortunately, during this outbreak, most of the isolates were sensitive to cotrimoxazole, ceftazidime, tigecycline, and levofloxacin and moderately sensitive to minocycline and meropenem. Many antibiotics which are used now against *B. cepacia* were not available at that time when *B. cepacia* was first isolated. Worldwide the epidemiology has changed from one a common and virulent infection to an infrequent but significant infection [2]. We had observed death in 60% of cases of *B. cepacia* infections in ICU patients. But, it remains unclear whether the mortality was due to *B. cepacia* or other co-morbid conditions in these patients. Thus, further studies are needed to be administered to deal with this issue. However, few assumptions are often made up by this study. The disease is no longer restricted to patients with CF and may affect patients in an ICU setting which the mortality from the infection remains high in our part of the globe. The adequacy of control measures was evaluated by follow-up of cases after the outbreak, both clinically and microbiologically. Control measures were considered adequate because new cases of Bcc sepsis stopped. Timely reporting of infection, implementation of infection control methods like hand hygiene, proper cleaning, and disinfection of SICU equipment, and cohorts of infected cases stopped this outbreak.

Limitation(s)

The limitations of the study were that it was a retrospective study. Prospective studies and involving more number of patients are important for future studies. Biochemical identification to differentiate between *B. cepacia* and *Chryseobacterium* was not carried out.

CONCLUSION(S)

The study highlights the importance of the identification of *Burkholderia cepacia* complex and its role in infection and outbreak. The study also highlights the importance of the active role of microbiologists and clinicians towards any sudden rise in infection rate. Timely

reporting of infection, implementation of infection control methods like hand hygiene, proper cleaning is of utmost importance.

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