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Clinical Spectrum of *Burkholderia cepacia* Infection in Cancer Patients: A Retrospective Study of an Emerging Disease

Sulav Sapkota[1*], Shobha K Ganesan[2], Mona Priyadarshini[3], Priyank Tripathi[4], Shoha Savitha A[5] and Somarat Bhattacharjee[6]

[1]Department of Hematology & Medical Oncology, HCG Hospital, Bengaluru 560 095, Karnataka, India

[2]Department of Microbiology, HCG Hospital, Bengaluru 560 095, Karnataka, India

[3]Department of Gynae-Oncology, HCG Hospital, Bengaluru 560 095, Karnataka, India

[4]Department of Pharmacology, HCG Hospital, Bengaluru 560 095, Karnataka, India

[5]Department of Microbiology, HCG Hospital, Bengaluru 560 095, Karnataka, India

[6]Department of Radiotherapy, HCG Hospital, Bengaluru 560 095, Karnataka, India

[*]**Corresponding author:** Sulav Sapkota, Senior Registrar, Department of Hematology & Medical Oncology, HCG Hospital, HCG Towers No.1, Kalinga Rao Road, Sampangiram Nagar, Bengaluru 560 095, Karnataka, India, Tel: 0091-9097711204; E-mail: dr.sulavsapkota@yahoo.com

Abstract

Aim: To study the epidemiology of *Burkholderia cepacia* infection in cancer patients.

Objectives:

•To study the patients characteristics features of Burkholderia infections.

•To study the characteristics features of *Burkholderia cepacia* infections.

•To study the pattern of antimicrobial sensitivity and resistance.

•To identify the cause of infection and reduce the risk of Hospital acquired infections.

Methods: This retrospective study was conducted from July 2017 to July 2018 at HCG Tertiary Cancer Hospital, Bangalore, India.

Results: Total 21 patients were diagnosed with BCC infection during the study period. Those affected were mostly Female patients (80%), admitted in medical ward for chemotherapy with mostly central lines.

In our study, the incidence of Burkholderia infection was mostly found with Blood Stream Infections (90%), mostly seen in those with central line associated blood stream infection (52%) and peripheral blood stream infection (38%). Before the incidence of infection, 11 patients (52%) had already been treated with higher antibiotics including Carbapenems. In our study, all patients (100%) could be salvaged with treatment and were discharged.

Conclusion: *Burkholderia cepacia* infection is one of the emerging infections in the tertiary cancer setting. Hospital Infection Control Committee's regular surveillance program and the training of healthcare workers are vital to reduce the hospital acquired infections.

Keywords: *Burkholderia cepacia*; Infection; Blood stream infection

Introduction

Hospital acquired infections (HAI) especially multi-drug resistant infections are one of the scandalous infection in tertiary cancer hospitals with major implications like morbidity, mortality, financial burden, longer duration of hospital stay, interruption as well as cessation of conventional treatment. Among them, *Burkholderia cepacia* is one of the emerging and challenging bug in our setting. Pseudomonas cepacia was originally described by William Burkholder in 1950 as the pathogen of bacterial rot of onion bulbs and was later integrated to the new genus Burkholderia in 1992 [1,2]. It is an aerobic, motile, glucose nonfermenting, multidrug resistant Gram-negative bacillus that proliferates under conditions of minimal nutrition. It is distributed ubiquitously and found most commonly on plant roots, soil and moist environments. It survives and multiplies in aqueous hospital environments, including detergent solutions and intravenous fluids, where it may persist for long periods [3]. It has transpired out to be a serious pathogen causing fatal necrotizing pneumonia and bacteremia, especially in patients with cystic fibrosis (CF) and chronic granulomatous disease [4]. Even though rare, B. cepacia infections can be severe, with mortality rates very high up to 83% among patients with lower respiratory tract infections [5,6].

In India, there are no accurate reports of the incidence as well as prevalence of Burkholderia infection due to deficient in specific laboratory tests and data collections. In majority of cases, these bacteria have been dubiously reported as Pseudomonas species. It has only been reported from few tertiary care centers in north India [7,8]. Our hospital data shows sporadic incidence of Burkholderia infections however this is the first time we are studying the clinical features of infections in our cancer patients for duration of one year.

Antibiotics treatments for BCC are very limited and include Ceftazidime and Carbapenems. Irrational use and abuse of these higher antibiotics has been a major concern especially in developing countries which have led to the emergence of Gram-negative isolates resistant to these agents [9,10]. Burkholderia is one of the multidrug resistant organisms (MDR) identified as an urgent threat to human health by the World Health Organization (WHO) and the US Center for Disease Control (CDC). Our hospital, being a multi-specialty cancer hospital, deals with immunocompromised patients and hence Burkholderia infection requires major scrutiny.

According to Grinbaum [11], "One of the objectives of Epidemiological Surveillance carried out by the Hospital Infection Control Service is to detect outbreaks before the propagation results in further harm." We have a similar body, named Hospital Infection

Control Committee (HICC) which is a committee responsible to investigate the infections that includes the source of the agent, means of transmission and control measures.

Materials and Methods

This retrospective study was conducted from July 2017 to July 2018 at HCG Hospital, KR Unit, and Bangalore, India which is a 200 bedded tertiary cancer hospital comprising of four towers.

An investigation into the predisposing causes was initiated, using computer based database and medical record department as the data source. Cases were defined as symptomatic patient with culture positivity for *Burkholderia cepacia*. All the blood cultures were done on automated Blood Culture System (Bact Alert) for blood and other samples were processed on routine media and then subjected to automated Vitek 2 Compactor for identification and antibiotic sensitivity pattern with MIC's value.

A number of predisposing factors and risk factors were included

1)Presence of neutropenia; 2) Central lines 3) Catheterization 4) Parenteral nutrition 5) Blood products 6) Intensive care unit (ICU) stay 7) Medical or surgical cases 8) Intubation/ventilation 9) Steroids use 10) Prior use of higher antibiotics.

A study preformat was created, which included patient identification, duration of hospitalization, culture reports as well as above selected predisposing factors.

After the collection of reports statistical analysis was done using SPSS Software.

Results

Total 21 patients were diagnosed with Burkholderia infection during the study period. The results of the investigation are presented in Tables 1-3.

Characteristics	Number of patients	Percentage %
Mean age	36	-
Female	17	80
Co-morbidity (DM)	4	19
International patients	3	14
Solid tumors	15	71
Haematological	6	29
Surgical cases	3	14
Medical cases	18	86

Table 1: Burkholderia investigation based on patient characteristics.

Characteristics	Number of patients	Percentage %
Fever	20	95
Neutropenic sepsis	7	33

	Number of patients	Percentage %
Blood stream infection (BSI)	19	90
Surgical site infection	1	5
Lower respiratory infection	0	-
Urinary tract infection	1	5
High procalcitonin level (>0.5)	5	24
Death	0	-

Table 2: Burkholderia investigation based on patient infections.

Factors	Number of patients	Percentage %
Neutropenia	8	38
Central lines	18	85
Surgical cases	3	14
ICU stay	4	19
Steroid use	20	95
Diabetic patients	4	19
Intubated/Ventilated	2	9
Blood products	11	52
Parenteral nutrition	2	9
Higher antibiotics used before	11	52
Urinary catheter	2	9

Table 3: Burkholderia investigation based on factors.

The incidence of nosocomial B. cepacia infections was very low in our hospital (0.28 per 1000 admission). In our study, most commonly affected were Females (80%) with blood stream infections (90%) followed by surgical site infection (5%) and urinary tract infection (5%). They were mostly medical cases on chemotherapy treatment. 85% of the patients had central line and 19% patients were admitted in ICU for further management. Only 9% of the cases were on ventilator support. Majority of the patients (52%) were being treated with higher antibiotics, including carbapenems, prior to this infection. Most of the infection incidence rate was found to be in Tower 1 as shown in Table 4.

Duration 1 year	Tower 1	Tower 2	Tower 3	Tower 4	Total
Number	12	2	5	2	21

Table 4: Infection incidence rates.

Among the patients, there were three international patients and eighteen national patients. Solid tumor cases were 15(71%) while hematological cases were 6(29%). Most common solid tumors were cancer breast 9(42%) and most common haematological cases were acute lymphocytic leukemia 4(19%). Mean age of the patients was 36 (range 2-56). Average duration of hospital stay during 7 the period was

10 days (range 1-52 days) while average duration of ICU stay was 3 days (range 1-6 days).

20 (95%) of the patients presented with febrile episodes during admission to the hospital. Only 7 patients were diagnosed with Neutropenia sepsis. Severity of fever episodes was mild to moderate up to 102°F. Procalcitonin level which is a marker of acute bacterial infection was found to be raised in 5 (24%) patients only. Both patients who went to ICU were having high procalcitonin value with one being highest level of 10.9 ng/ml. 20 (95%) patients had received low dose steroids usually dexona as a antiemetic as predications and post chemotherapy duration for average of about four days in each cycles of chemotherapy [11]. (52%) patients had received blood transfusions before the infections which were transfused mainly by the use of central lines only.

Due to technical reasons, it was not possible to carry out molecular typing, however, all of the positive culture samples had the same phenotypic antibiogram profile which is depicted in Table 5. The antimicrobial resistance rates among B. cepacia strains were found to be high in our study. The most active anti-microbial agents against B. cepacia isolates were ceftazidime, minocycline and carbapenems. Antibiotics escalations as well as de-escalations were done after the antibiogram reports. Central lines were removed immediately on next day after the culture reports. Most common antibiotics used during the treatment were Meropenem 17(80%) and Ceftazidime 4(20%). All the patients (100%) recovered with the treatment and were discharged.

Antimicrobial	MIC (microg/ml)	Interpretation
Ceftazidime	4	Sensitive
Piperacillin/ Tazobactum	>=128	Resistant
Cefoperazone/ Sulbactum	>=64	Resistant
Imipenem	>=16	Resistant
Meropenem	4	Sensitive
Amikacin	>=64	Resistant
Gentamycin	>=16	Resistant
Colistin	>=16	Resistant
Minocycline	8	Intermediate

Table 5: The antimicrobial resistance rates.

Discussion

In the literature, reports of nosocomial B. cepacia infections are restricted to the epidemics [12]. Our data do not show any epidemics, but all sporadic cases of B. cepacia infections. The incidence of nosocomial B. cepacia infections was very low in our hospital (0.28 per 1000 admission). Tower 1 Medical wards were the wards in which nosocomial B. Cepacia infections occurred more frequently in our study. During that period of time, construction and renovations of the building was going on that might have led to increase in the infection. It might be possible cross-contaminations might have happened from one tower to another tower due to change in the shift of healthcare workers in the respective towers.

The most frequent risk factor in these patients were invasive procedures mostly central lines insertion like chemo port as well as peripherally inserted central catheter (PICC). As central lines are essential in our patients for long term chemotherapy infusions, infection of central lines might happen during the insertion procedure as well as during the maintenance period. Biofilms formation in the central lines might cause bacteria to harbor and cause central lines associated blood stream infections. Blood products through central lines might help in formation of Biofilms that might cause central lines infections in our cases.

Cancer itself is an immunocompromised state. Besides, patients will receive chemotherapy as well as lots of immunosuppressant drugs that cause low immunity of the patients. Hence, they are vulnerable to opportunistic infections like Burkholderia which is itself non-harmful to healthy persons. Long term use of steroids also causes increase in the rate of infections due to deranged cellular immunity. Neutropenia will be caused by chemotherapy due to myelosuppression during the treatment. Neutropenia might results in Neutropenic sepsis which is an oncological emergency. Diabetes itself causes increase in infection due to deranged blood sugar level in the patients. All the above predisposing factors were found to be present in our cases that might have resulted in Burkholderia infections.

B. cepacia is an established pathogen that is inherently resistant to aminoglycosides as well as first and second-generation cephalosporins. The multi-drug resistance of B. cepacia has been credited to an impermeable selective outer membrane, an efflux pump mechanism, and/or the production of an inducible chromosomal beta-lactamase [13-15]. The antimicrobial resistance rates among B. cepacia strains were found to be high in our study. However, we could use sensitive antibiotics to our patients as per the antibiogram and we could salvage all the patients.

We concede nonavailability of technologies like pulse field gel electrophoresis (PFGE) or multilocus sequence typing (MLST) in our hospital setting as a limitation in proving clonal relatedness of all isolates found during the study period.

Conclusion

Burkholderia cepacia infection is one of the emerging infections in the multi-speciality cancer setting. Hospital Infection Control Committee's regular surveillance program and the training of healthcare workers are vital to reduce the [11] hospital acquired infections. The determining factor for Central lines infections appears to be hand hygiene of the healthcare workers. Hence, strict hand wash and PPE must be followed as per the Hospital Infection Control Committee policies. Antimicrobial stewardship is an important part of efforts to control multidrug resistant organisms.

Conflict of interest: This study has no potential conflict of interest.

Disclosures: All procedures performed in studies were in accordance with the ethical standards of the institutional.

Informed consent: Informed consent was obtained from all individual participants included in the study.

References

1. Burkholder W (1950) Sour skin, a bacterial rot of onion bulbs. Phytopathology 40: 115-118.

2. LiPuma JJ, Lum GD, Vandamme P (2007) Burkholderia, Stenotrophomonas, Ralston nia, Cupriavidus, Pandoraea, Brevundimonas, Comamonas and Acidovorax. Manual of Clinical Microbiology. Washington, DC.

3. Doit C, Loukil C, Simon AM, Ferroni A, Fontan JE, et al. (2004) Outbreak of *Burkholderia cepacia* bacteremia in a pediatric hospital due to contamination of lipid emulsion stoppers. J Clin Microbiol 42: 2227-2230.

4. Siddiqui AH, Mulligan ME, Mahenthiralingam E, Hebden J, Brewrink J, et al. (2001) An episodic outbreak of genetically related *Burkholderia cepacia* among non-cystic fibrosis patients at a university hospital. Infect Control Hosp Epidemiol 22: 419-422.

5. Jarvis WR, Olson D, Tablan O, Martone WJ (1987) The epidemiology of nosocomial Pseudomonas cepacia infections: Endemic infections. Eur J Epidemiol 3: 233-236.

6. Maningo E, Watanakunakorn C (1995) Xanthomonas maltophilia and Pseudomonas cepacia in lower respiratory tracts of patients in critical care units. J Infect 31: 89-92.

7. Gautam V, Ray P, Puri GD, Sharma K, Vandamme P, et al. (2009) Investigation of *Burkholderia cepacia* complex in septicaemic patients in a tertiary care hospital, India. Nepal Med Coll J 11: 222-224.

8. Gautam V, Ray P, Vandamme P, Chatterjee SS, Das A, et al. (2009) Identification of lysine positive non-fermenting gram negative bacilli (Stenotrophomonas maltophilia and *Burkholderia cepacia* complex). Indian J Med Microbiol 27: 128-133.

9. Kontopidou F, Plachouras D, Papadomichelakis E, Koukos G, Galani I, et al. (2011) Colonization and infection by colistin-resistant Gram-negative bacteria in a cohort of critically ill patients. Clin Microbiol Infect 17: E9–E11.

10. Matthaiou DK, Michalopoulos A, Rafailidis PI, Karageorgopoulos DE, Papaioannou V, et al. (2008) Risk factors associated with the isolation of colistin-resistant gram-negative bacteria: A matched case-control study. Crit Care Med 36: 807-811.

11. Pereira CR, Levin ASS, Schout D (2000) Grinbaum RS Vigilância Epidemiológica de Infecções Hospitalares. Manual de Epidemiologia Aplicada ao Controle de Infecções Hospitalares em Hospitais e Serviços Correlatos, S.P. APECIH 2000.

12. Nasser RM, Rahi AC, Haddad MF, Daoud Z, Irani-Hakime N, et al. (2004) Outbreak of *Burkholderia cepacia* bacteremia traced to contaminated hospital water used for dilution of an alcohol skin antiseptic. Infect Control Hosp Epidemiol 25: 231-239.

13. Burns JL, Wadsworth CD, Barry JJ, Goodall CP (1996) Nucleotide sequence analysis of a gene from Burkholderia (Pseudomonas) cepacia encoding an outer membrane lipoprotein involved in multiple antibiotic resistance. Antimicrob Agents Chemother 40: 307-313.

14. Aronoff SC (1988) Outer membrane permeability in Pseudomonas cepacia: Diminished porin content in a beta-lactam-resistant mutant and in resistant cystic fibrosis isolates. Antimicrob Agents Chemother 32: 1636-1639.

15. Trépanier S, Prince A, Huletsky A (1997) Characterization of the penA and penR genes of *Burkholderia cepacia* 249 which encode the chromosomal class A penicillinase and its LysR-type transcriptional regulator. Antimicrob Agents Chemother 41: 2399-2405.