JPSIM Journal of Pakistan Society of Internal Medicine

Review Article

Burkholderia Cepacia Complex- Evolution and Spectrum

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How to cite this:

Fatima T, Shakoor S. Burkholderia Cepacia Complex- Evolution and Spectrum. J Pak Soc Intern Med. 2022;3(1):3-6

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DOI: https://doi.org/10.70302/jpsim.v3i1.2202

Introduction

Burkholderia cepacia complex (BCC) is a group of Gram-negative bacteria, widely distributed in natural and hospital environments.[1] These gram-negative rods, non-lactose fermenters, motile, aerobic and often resistant to multiple antibiotics. Burkholderia cepacia was previously recognized as Pseudomonas cepacia. Later, other human, plant and environmental pathogens with similar molecular taxonomy led to formation of new genus Burkholderia, comprising over 50 species.[2] They are commonly found as a part of natural environment which can be attributed to their extraordinary ability to survive harsh conditions and their nutritional versatility.[3] In the 1990s, it was recognized that B. cepacia should be named the B. cepacia complex (BCC) as it may consist of variety of several phenotypically related but genetically different microorganisms. Five genomovars initially identified, were B. cepacia (genomovar I), B. multivorans (genomovar II), B. cenocepacia (genomovar III), B. stabilis (genomovar IV), B. vietnamiensis (genomovar V).[4] BCC has undergone dramatic taxonomic changes in last few decades and now exhibits an extensive diversity of genotypes composed of at least 20 genetically distinct genomic species associated with different levels of severity and transmissibility, including, B. cepacia (genomovar I), B. multivorans (genomovar II), B. cenocepacia (genomovar III), B.stabilis (genomovar IV), B. vietnamiensis (genomovar V),B. dolosa (genomovar VI), Burkholderia ambifaria (genomovar VII), Burkholderia anthina (genomovar VIII),and Burkholderia pyrrocinia (genomovar IX) etc.[3,5,6]

Spectrum of Infection

The evolution in the nomenclature of these bacteria can be attributed to their emergence as significant opportunistic pathogens, particularly in cystic fibrosis (CF), chronic granulomatous disease, which are the commonest risk factors for disease acquisition, where heavy lung colonization and consequent severe lung infections, necrotizing pneumonia, septicemia, in these patients have been associated with poor outcomes[7,8] Moreover, it has emerged as an important and frequent opportunistic and nosocomial pathogen in hospitalized and immunocompromised patients, with crude mortality rates reported as high as 53.8 %.[7] Elevated SOFA score, diabetes, inappropriate initial empirical antimicrobial therapy and malignancy are important predictors of adverse outcome in such patients with BCC bacteraemia.[9,10]

Neonatal Infections

BCC have also been increasingly reported as a cause of neonatal sepsis.[11] Prematurity, very low birth weight, frequent use of broad spectrum antibiotics, peripheral and central intravenous catheters, total parenteral nutrition, predispose these neonates to BCC sepsis. In neonates, a case fatality rate of 17% has been reported.[12] High mortality rates can be attributed to limited therapeutic options and emerging antimicrobial resistance (AMR) as well as virulence factors of the bacteria itself. Existing renal failure on hemodialysis, numerous pulmonary or bronchoscopic procedures, recent abdominal surgery have been seen to be associated with the development of B. cepacia bacteremia, while protracted ventilatory requirement, frequent nebulization, and usage of beta-lactam, aztreonam, macrolide, vancomycin antibiotics have been identified as a cause for respiratory tract colonization of B. cepacia.[13,14] Prolonged intensive care unit stay is another identified risk factor for nosocomial transmission of BCC infection.[7]

Virulence Factors

BCC is known to produce extracellular lipase, metalloproteases, serine proteases which help in interaction with epithelial cells and cellular invasion. Lipopolysaccharide (LPS) alongwith inducing a robust immune response contributing to host cell damage, together

with flagella and pili are imperative in communication with the Cystic Fibrosis host. Flagella, pili, adhesins are vital to mediate attachment to the host cells and also aid in maintaining motility. One conventional LuxIR quorum-sensing (QS) system, named CepIR, is usually found in every BCC species which offers a machinery for prompt adaptation to environmental variations, involved in production of toxin, proteases, superoxide dismutase, siderophore (pyochelin, salicylic acid, cepabactin, and ornibactin). Swarming motility and development of biofilm can also be attributed to Quorum sensing in Bcc[15]. Genomovar I strains also produce melanin and exopolysaccharide which may contribute to pathogenicity and virulence.

Genomovar Distribution

Despite their genetic similarity, there is great variation in genomovar-specific disease epidemiology in different populations, and in different parts of the world, for instance, between CF and non-CF patients. B. cenocepacia has been the most prevalent genomovar in patients with CF in the past and has been replaced by B. multivorans with passing years, whereas, B. cepacia genomovar I is the least common.[3,14,16] B.cenocepacia genomovar III is also the most common genomovar causing bacteremia in non-CF patients in critical care settings.[14,17] Given the variation in genomovar distribution in non-CF populations and geographical locations, predominance of any one genomovar cannot be assumed to be the prevalent genomic species in neonatal population as it hasn't been investigated much. However, according one study conducted in Karachi confirms the dominance of B. cepacia genomovar I in neonatal population[18]. The variability and predilection of certain genomovars to certain populations leads to the hypothesis that the transmissibility varies for different genomovars of BCC. Therefore, molecular characterization of bacterial isolates is vital for epidemiological breakdown of bacterial pathogens and subspecies.

Outbreaks

The BCC are known for their nutritional variance and ability to grow and flourish in diverse environments; some are even capable of breaking down important pollutants and penicillin G to use as a source of carbon.[19] As a result, BCC is actively reported for causing outbreaks in hospital setups. An integrated review published in 2020 reviewed 125 documented outbreaks and the causes identified in most of the BCC nosocomial outbreaks (74.4%) included medication vials, purifiers, sanitizers and antiseptics.[20] Contaminated heparin injections, nebulized salbutamol, oxygen humidifier, ventilator water traps, chlorhexidine disinfectants solution, mouthwash, reusable albuterol vials, enteral feeding dyes, bottled and unbottled water, table linen, nasal sprays and ultrasound gels were recognized in multiple outbreaks as a source of BCC.[21-24] Potential reservoirs of B. cepacia identified include the water containers of incubator humidifiers, water used for humidification in nebulizers and respiratory devices, tap water, wash-hand basin and drains, incubator tops, antibacterial products, and fluids used in parenteral nutrition. In any case outbreaks are likely to happen due to various dysfunctions like malfunctioning of autoclaving, inadequate cap decontamination, multiple use of an open bottle of fluids, prolonged duration of infusion and the vulnerability of the patients such as low birth weight, congenital diseases and immunodeficiencies. Contaminated disinfectant products used for cap decontamination can also lead to contamination. Post autoclaving contamination is another neglected cause and risk factor.[24]

Outbreaks have been reported earlier from various neonatal intensive care units (NICU). An outbreak of BCC pseudobacteraemia was reported from a neonatal intensive care unit which was caused by commercially available chlorhexidine which turned out to be contaminated.[25] In another BCC neonatal outbreak, the source was tracked to intravenous solutions of 5 % dextrose, opened vials of normal saline and continuous positive airway pressure humidifier water.[26] A 7-month outbreak of nosocomial Burkholderia cepacia bacteremia involving eight children in a pediatric hospital was found to be associated to the upper surface of capped rubber stoppers of bottles of a commercial lipid emulsion used for parenteral nutrition.[27] BCC outbreaks have also been reported from Karachi.[28] Subsequent to these outbreaks, BCC has become a frequent isolate from bacteremic episodes among neonates admitted to NICUs in Karachi.[28]

Infection Prevention

Neonatal sepsis is a universal concern with high morbidity and mortality. The highest burden of neonatal sepsis is encountered in developing and underdeveloped countries where it is responsible for more than 50% of neonatal deaths, due to poor health system and infrastructure.[29] With increasing antibiotic usage and emergence of antimicrobial resistance, BCC outbreaks are becoming common. However, strong infection prevention and control measures have proven to be effective in decreasing the spread. Hand-washing is essentially basic and imperative in controlling healthcare-associated infections yet other hygienic measures like frequent environmental cleaning with hypochlorite to reduce bio-burden, proper terminal cleaning of bedside, prevention of formation of biofilms in the patients' surrounding, use of clean sterile water in humidifiers, appropriate cleaning of equipment, waste disposal all are necessary to reduce the transmission and acquisition of BCC infections. Different strategies have been imple-

mented in controlling these outbreaks. A study showed BCC was effectively eliminated from the neonatal unit by using recurrent thermal shock (hot water at 65°C for 10 min), changing taps to touch free taps and cleaning sinks with hypochlorite.[30] In any case epidemiological investigations are vital to identify the source and course of infection in outbreaks.

Treatment

According to CLSI 2021 Meropenem, Levofloxacin, Trimethoprim Sulfamethoxazole, Ceftazidime are first line agents. Minocycline and Ticarcillin- clavulanate are considered second line agent.[31] However, in vitro susceptibility results have shown resistance to TMP-SMX and ceftazidime in BCC isolate, around 10 to 40% and 30 to 40% respectively.[32] In this scenario, it's best that the antimicrobial therapy should be directed by in vitro susceptibility results where available; and combination therapy should be used for treatment of multidrug resistant BCC infections

Conclusion

The analysis highlights the variable disease presentation, propensity to cause outbreaks and importance of infection prevention measures for BCC infections.

Conflict of Interest: None

Funding Source: None

References

1. Tseng SP, Tsai WC, Liang CY, Lin YS, Huang JW, Chang CY, Tyan YC, Lu PL. The contribution of antibiotic resistance mechanisms in clinical Burkholderia cepacia complex isolates: an emphasis on efflux pump activity. PLoS One 2014; 9(8):e104986.
2. Leitão JH, Sousa SA, Ferreira AS, Ramos CG, Silva IN, Moreira LM. Pathogenicity, virulence factors, and strategies to fight against Burkholderia cepacia complex pathogens and related species. Applied Microbiol Biotechnol. 2010;87(1):31-40.
3. LiPuma JJ. Update on the Burkholderia cepacia complex. Curr Opin Pulm Med. 2005; 11(6):528-33.
4. Jin Y, Zhou J, Zhou J, Hu M, Zhang Q, Kong N, Ren H, Liang L, Yue J. Genome-based classification of Burkholderia cepacia complex provides new insight into its taxonomic status. Biology Direct. 2020;15(1):1-4.
5. Bach E, Sant'Anna FH, Magrich dos Passos JF, Balsanelli E, de Baura VA, Pedrosa FO, et al. Detection of misidentifications of species from the Burkholderia cepacia complex and description of a new member, the soil bacterium Burkholderia catarinensis sp. Pathog Dis. 2017;75(6): 1-8.
6. Ong KS, Aw YK, Lee LH, Yule CM, Cheow YL, Lee SM. Burkholderia paludis sp. nov., an Antibiotic-Siderophore Producing Novel Burkholderia cepacia Complex Species, Isolated from Malaysian Tropical Peat Swamp Soil. Front Microbiol. 2016; 7(12): 2046.
7. Dizbay M, Tunccan OG, Sezer BE, Aktas F, Arman D. Nosocomial Burkholderia cepacia infections in a Turkish university hospital: a five-year surveillance. J Infect Dev Ctries 2009; 3(04):273-7.
8. Van Laer F, Raes D, Vandamme P, Lammens C, Sion JP, Vrints C, Snoeck J, Goossens H. An outbreak of Burkholderia cepacia with septicemia on a cardiology ward. Infect Cont Hospital Epidemiol. 1998; 19(2): 112-3.
9. Mahenthiralingam E, Urban TA, Goldberg JB. The multifarious, multireplicon Burkholderia cepacia complex. Nature Reviews Microbiology. 2005; 3(2): 144-56.
10. Ku NS, Han SH, Kim CO, Baek JH, Jeong SJ, Jin SJ, Choi JY, Song YG, Kim JM. Risk factors for mortality in patients with Burkholderia cepacia complex bacteraemia. Scand J Infect Dis. 2011; 43(10):792-7.
11. Patra S, Bhat R, Lewis LE, Purakayastha J, Sivaramaraju VV, Mishra S..Burkholderia cepacia sepsis among neonates. Indian J Pediatr. 2014; 81(11):1233-6.
12. Chandrasekaran A, Subburaju N, Mustafa M, Putlibai S. Profile of neonatal sepsis due to Burkholderia cepacia complex. Indian Pediatr 2016; 53(4):1109-10
13. Abdallah M, Abdallah HA, Memish ZA. Burkholderia cepacia complex outbreaks among non-cystic fibrosis patients in the intensive care units: a review of adult and pediatric literature. Infez Med. 2018; 26(4):299-307.
14. Bressler AM, Kaye KS, LiPuma JJ, Alexander BD, Moore CM, Reller LB, Woods CW. Risk factors for Burkholderia cepacia complex bacteremia among intensive care unit patients without cystic fibrosis: a case-control study. Infection Control & Hospital Epidemiology. 2007; 28(8):951-8.
15. Lee JK. Two outbreaks of Burkholderia cepacia nosocomial infection in a neonatal intensive care unit. J Paediat Child Health. 2008; 44(1-2):62-6.
16. Pope CE, Short P, Carter PE. Species distribution of Burkholderia cepacia complex isolates in cystic fibrosis and non-cystic fibrosis patients in New Zealand. J Cyst Fibros. 2010; 9(6):442-6.
17. Gautam V, Ray P, Puri GD, Sharma K, Vandamme P, Madhup SK, et.al. Investigation of Burkholderia cepacia complex in septicemia patients in a tertiary care hospital, India. Nepal Med Coll J. 2009; 11(4):222-4.

18. Fatima T, Khan E, Nasir A, Alidina S, Malik F, Arif S, Irfan S, Qureshi SM, Shakoor S. Predominance of Genomovar I among Burkholderia cepacia Complex bacteremia in the Neonatal Population–a study from Karachi, Pakistan. Infect Dis J Pakistan. 2020; 29(2): 31-46.
19. Doit C, Loukil C, Simon AM, Ferroni A, Fontan JE, Bonacorsi S, et.al. Outbreak of Burkholderia cepacia bacteremia in a pediatric hospital due to contamination of lipid emulsion stoppers. J Clin Microbiol. 2004; 42(5):2227-30
20. Shaban RZ, Sotomayor-Castillo C, Nahidi S, Li C, Macbeth D, Mitchell BG, Russo PL. Global burden, point sources, and outbreak management of health-care-associated Burkholderia cepacia infections: An integrative review. Infect Control Hospital Epidemiol. 2020; 41(7):777-83.
21. Van Laer F, Raes D, Vandamme P, Lammens C, Sion JP, Vrints C, Snoeck J, Goossens H. An outbreak of Burkholderia cepacia with septicemia on a cardiology ward. Infect Control Hospital Epidemiol. 1998; 19(2): 112-3.
22. Ghazal SS, Al-Mudaimeegh K, Al Fakihi EM, Asery AT. Outbreak of Burkholderia cepacia bacteremia in immunocompetent children caused by contaminated nebulized sulbutamol in Saudi Arabia. American journal of infection control. 2006 Aug 1; 34(6):394-8.
23. Song JE, Kwak YG, Um TH, Cho CR, Kim S, Park IS, Hwang JH, Kim N, Oh GB. Outbreak of Burkholderia cepacia pseudobacteraemia caused by intrinsically contaminated commercial 0.5% chlorhexidine solution in neonatal intensive care units. J Hospital Infect. 2018; 98(3):295-9.
24. Bhise SM, Rahangdale VA, Qazi MS. Burkholderia Cepacia an emerging cause of septicemia-an outbreak in a neonatal Intensive Care Unit from a tertiary care hospital of central India. IOSR J Dent Med Sci. 2013; 10(4):41-3.
25. Pegues CF, Pegues DA, Ford DS, Hibberd PL, Carson LA, Raine CM, Hooper DC. Burkholderia cepacia respiratory tract acquisition: epidemiology and molecular characterization of a large nosocomial outbreak. Epidemiology & Infection. 1996 Jun; 116(3):309-17.
26. Salah A, Al-Subol I, Hudna A, Alhaj A, Alqubaty AR, Farie W, Sulieman D, Alnadhari O, Alwajeeh T, Alobathani F, Almikhlafy A. Neonatal sepsis in Sana'a city, Yemen: a predominance of Burkholderia cepacia. BMC Infect Dis. 2021; 21(1):1-0.
27. Bressler AM, Kaye KS, LiPuma JJ, Alexander BD, Moore CM, Reller LB, Woods CW. Risk factors for Burkholderia cepacia complex bacteremia among intensive care unit patients without cystic fibrosis: a case-control study. Infect Control Hosp Epidemiol. 2007; 128(08):951-8.
28. Qamar S, Noman F, Shamim S, Nadeem A, Ansari N, Chohan N, Qureishi A.Investigation of Burkholderia cepacia outbreak in a neonatal intensive care unit. Infect Dis J Pak. 2010; 19(2):167-71
29. Paul LM, Hegde A, Pai T, Shetty S, Baliga S, Shenoy S. An outbreak of Burkholderia cepacia bacteremia in a neonatal intensive care unit. Indian J Pediat. 2016; 83(4):285-8.
30. Kotsanas D, Brett J, Kidd TJ, Stuart RL, Korman TM. Disinfection of Burkholderia cepacia complex from non-touch taps in a neonatal nursery. J Perin Med. 2008; 36(3):235-9.
31. Tamma PD, Fan Y, Bergman Y, Sick-Samuels AC, Hsu AJ, Timp W, Simner PJ, Prokesch BC, Greenberg DE. Successful treatment of persistent Burkholderia cepacia complex bacteremia with ceftazidime-avibactam. Antimicrobial Agents Chemo. 2018; 62(4): e02213-17.
32. Liao CH, Chang HT, Lai CC, Huang YT, Hsu MS, Liu CY, Yang CJ, Hsueh PR. Clinical characteristics and outcomes of patients with Burkholderia cepacia bacteremia in an intensive care unit. Diagnost Microbiol Infect Dis. 2011; 70(2):260-6.
33. Jarvis WR, Highsmith AK, Allen JR, Haley RW. Polymicrobial bacteremia associated with lipid emulsion in a neonatal intensive care unit. Pediatr Infect Dis. 1983; 2(3):203-8.