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Review Article

Burkholderia Cepacia Complex- Evolution and Spectrum

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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.

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