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Epidemiology, microbiological, clinical characteristics, and outcome of *Burkholderia cepacia* complex infections in non-cystic fibrosis adult patients from Qatar

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ABSTRACT

Objectives: *Burkholderia* species infections are associated with diverse and challenging clinical presentations because of distinct virulence and antimicrobial resistance factors. The study aims to evaluate the epidemiology, microbiological, and clinical outcomes of *Burkholderia cepacia* complex (Bcc) infections in non-cystic fibrosis (CF) patients from Qatar.

Methods: A retrospective study was conducted on adult patients across all hospitals at Hamad Medical Corporation between January 2012 and December 2018 to evaluate clinically relevant Bcc in non-CF adult patients.

Results: Over 7 years, 72 episodes of *Burkholderia* species infections were recorded, 64 were secondary to Bcc primarily affecting males (78.12%) with a mean age of 53 years, from the Middle and Southeastern region (92.2%) affected predominantly by diabetes mellitus (34.4%), chronic kidney (23.4%), coronary heart (20.3%), and hypertensive diseases (17.2%) while recent hospitalization and admission to critical care were evident in 45.3% and 93.8% of cases, respectively. Main infection sites were urinary (43.8%) and respiratory (29.7%) with associated bacteremia recorded in 26.6% of cases. Microbiological characteristics demonstrated high-level resistance profiles leading to delayed microbiological clearance in case of bacteremia (61%) and management with multiple therapeutic agents (range 4-6) resulting in disease resolution in 90.6% of cases with observed 30-day mortality of 7.8%.

Conclusions: *B. cepacia* infections are infrequent, recorded mainly in middle-aged males with chronic comorbidities presenting as urinary, respiratory, and bacteremia associated with hospitalization, admission to critical care, and invasive procedures. High-level antimicrobial resistance is observed necessitating multiple therapeutic agents and suboptimal bacteriological clearance.

Introduction

Burkholderia is a group of rod-shaped motile obligate Gram-negative bacteria that are ubiquitous in water, soil, and plants. The genus Burkholderia encompasses around 80 species but clinically relevant human pathogens are only three; Burkholderia mallei, responsible for causing the historic Glanders disease, *B. pseudomallei*, capable of causing acute as well as chronic forms of severe and serious endemic disease such as melioidosis as well as *B. cepacia* complex (Bcc) which has been classically associated of causing debilitating recurrent pulmonary infections in patients with cystic fibrosis (CF) [1].

The epidemiological distribution of Burkholderia species such as *B. pseudomallei*, relates to pathogen, environmental as well as host factors that affect disease patterns in different regions around the world with established endemicity [1]. However, Bcc are more ubiquitous pathogens found in different environmental aspects in the community as well as healthcare settings leading to infrequent but worrisome healthcare-associated infections (HCAIs) [2,3]. Besides infecting patients with CF leading to debilitating disease, the spectrum of presentation in patients without CF is diverse affecting mainly vulnerable populations such as patients with chronic or critical conditions and the immune-compromised clinically manifesting

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as pneumonia, meningitis, urinary tract and bloodstream infections (BSIs) [1,4,5].

Following pathogens isolation, microbiological assessment to guide appropriate management proves extremely challenging, since the striking features of *Burkholderia* species infections in general and Bcc in particular, manifest in its notorious ability to resist multiple antimicrobial agents leading to paucity of therapeutic options as well as increased morbidity and mortality [5–7]. The underlying antimicrobial resistance mechanisms are multifactorial, for example, the pathogen has a unique modified lipopolysaccharide cell wall that hinders antimicrobial permeability and attachment for multiple classes leading to cell wall mediated resistance including the broad spectrum polymyxins class that effectively targets a broad range of Gram-negative bacteria. Similarly, the pathogen harbors potent B-lactamase genes capable of inactivating various penicillin-based antibiotics such as basic and advanced classes of βlactams, monobactams, βlactams βlactamase inhibitors (BLBLIs), cephalosporins as well as the advanced carbapenems. Equally, other resistance mechanisms such as efflux pumps, and modifying and altered drug targets also produce resistance to carbapenems, aminoglycosides, and quinolones rendering the organism one of the most challenging multidrug-resistant bacteria [5,8,9]. These principal features of a high antibiotic resistance profiles, project Burkholderia-related infections as maladies of significant morbidity and mortality estimated as high as 50% in reviews of multiple outcome studies [10].

Despite the importance of management of infection caused by Bcc; there is a paucity of information about the epidemiology, microbiological, and clinical characteristics as well as outcomes of infected patients in different regions around the world particularly in non-CF patients. Most reported cases in the literature are derived from cohorts' studies or in the context of outbreaks mostly in patients with serious underlying diseases, in intensive care settings, or following invasive procedures [10]. Regionally, there are no previous studies to outline the scale of the problem or to examine different aspects of the disease spectrum. To cover the outlined gap, the presented study aimed to evaluate the epidemiology, microbiological, clinical as well as outcomes of Bcc infections in non-CF adult patients in secondary and tertiary care settings in Qatar.

Methodology

Settings

The retrospective study was conducted in secondary and tertiary care settings at Hamad Medical Corporation (HMC), Doha, Qatar between January 1, 2012, and December 31, 2018, comprising 7 years review. The HMC covers almost the entire population of the country of around 3 million population through 14 acute and specialized care hospitals with a total bed capacity of almost 2500 [11,12].

Microbiological identifications, and antimicrobial susceptibility tests

Confirmed culture-positive cases of clinically relevant *Burkholderia* species were identified using standard microbiological techniques at the central microbiology laboratory of HMC which complies with local and international standards including regular inspection and accreditation. Microbial identifications, confirmation, and antimicrobial susceptibility tests (AST) were performed using automated BD Phoenix^{TM} system (BD Diagnostics, Durham, NC, USA) and Matrix-Assisted Laser Desorption Ionization Time of Flight Mass Spectrometry (MALDI-TOF MS) of Bruker Daltonics MALDI Biotyper (Billerica, MA, USA) according to the manufacturer's recommendations while additional ASTs were performed with E test according to manufacturer recommendations. For BSIs, microbiological clearance was defined by negative cultures following 72 hours of initiation of directed antimicrobial therapy.

Procedure and data collection

Patients' clinical and laboratory data were retrospectively retrieved from the electronic healthcare system. Obtained data covered, demographic variables, comorbidities, clinical presentations, potential risk factors, infection sites, clinical course including admission to critical care, as well as microbiological data, antimicrobial treatment, and all complications and outcomes including, 30-day mortality.

Ethical approval and data management

The study was approved by the Medical Research Centre (MRC) of HMC as well as the Institution Review Board which abides by policies and regulations in line with regional and international standards (Protocol: MRC: 01-18-388). Primary data were only accessed by primary investigators and data management was observed according to regulations.

Statistical analysis

Statistical analysis was performed using Stata statistical software, version 16.1 (Stata Corporation, College Station, TX, USA). Continuous variables were presented as mean and standard deviation while categorical variables were presented as total number and percentages. Incidence was calculated for yearly reported episodes in relation to the total local population at the time. Descriptive statistics such as means, standard deviations, and percentages were used to summarize and describe the characteristics of the study population, including demographics, comorbidities, and clinical outcomes.

Results

Epidemiological, clinical, and outcomes characteristics

During the outlined study period 72 *Burkholderia* species were identified (64 were Bcc, six *B. pseudomali*, one *B.gladioli,* and one *B. fungorum*), and the incidence of Bcc yearly episodes ranged between 0.38 per 100.000 population in 2012 to 0.54 per 100.000 population in 2018 as depicted in Figure 1. Of the examined clinical episodes of Bcc infections (64), the majority of patients were males (78.12%) aged between 46-64 (44.4%) with a mean age of 53.4, predominantly from Middle and Southeastern region (92%) while diabetes mellitus (34%), chronic kidney disease (23%), coronary heart diseases (20%), and hypertension (17%) were the predominant comorbidities. Observed major risk factors were recent hospitalization (45%), recent surgical procedure (30%), stone formation (22%), and mechanical ventilation (20%) Table 1. Main infection sites were urinary (44%) and respiratory (30%) while associated bacteremia was recorded in 27% of cases Table 1. Admission to critical care was recorded in 94% of cases with complete resolution of symptoms occurring in 91% with relapses recorded in 11% while the 30-day mortality was observed in 8% of cases Table 2. The majority of patients (73%) received empiric then tailored antibiotic therapy comprising meropenem (50%), ceftazidime (37.5%), cotrimoxazole (37.5%), and piperacillin-tazobactam (25%) with 45% of patients receiving combination therapy of multiple antimicrobial agents' combinations Table 2.

Microbiological characteristics

Microbiological characteristics showed diverse antimicrobial resistance spanning all classes at 90% Table 3 necessitating multiple therapeutic agents ranging from 4-6 for management Table 2. Reporting of susceptibility to antibiotics was not uniform among the sample since additional agents AST was performed for more resistant pathogens. The highest antimicrobial susceptibilities were reported for cotrimoxazole (94%, 59/63), meropenem (93%, 26/28), ceftazidime

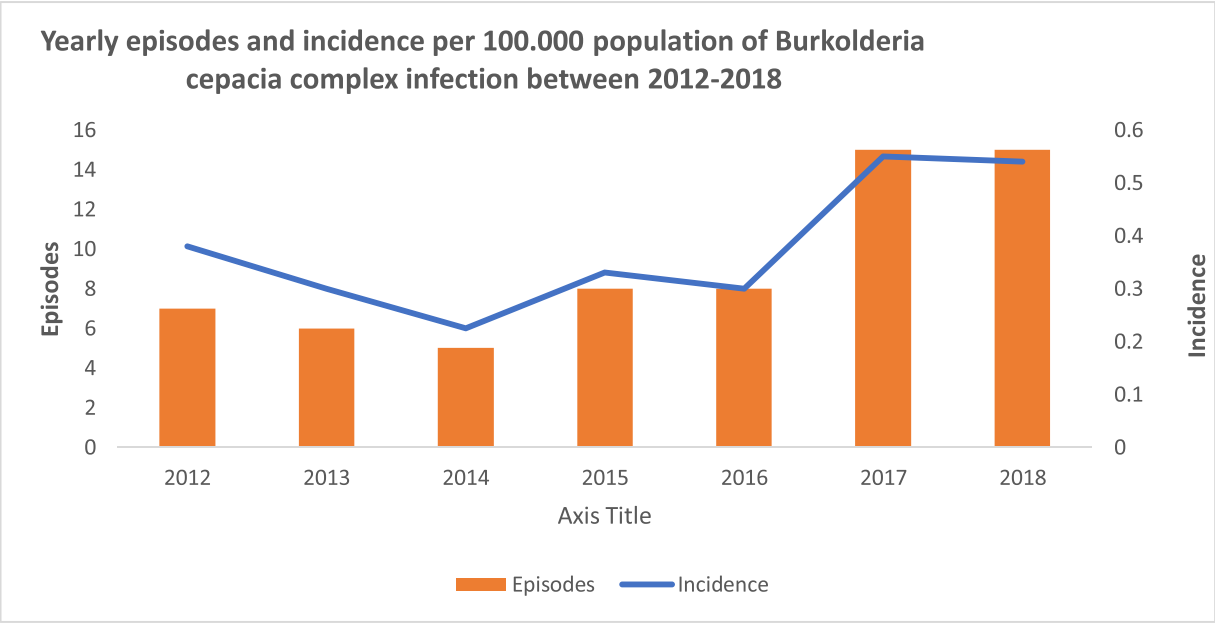

Figure 1. Burkholderia cepacia complex infections.

Table 1
Baseline characteristics of the studied cohort (N = 64).

Parameter	Value N (%)
Demography	
Age years (mean ± SD)	53.42 ± 16.63
Sex n (%)	
Male	50 (78.12)
Female	14 (21.87)
Nationality by World Health Organization region of origin n (%)	
Eastern Mediterranean region	38 (59.37)
Southeast Asian region	21 (32.81)
European region	2 (3.12)
Western Pacific regions	2 (3.12)
African region	1 (1.56)
Comorbidities n (%)	
Diabetes mellitus	22 (34.37)
Chronic kidney disease	15 (23.43)
Cardiovascular diseases	13 (20.31)
Hypertension	11 (17.18)
Malignancy	10 (15.62)
Chronic liver disease	4 (6.25)
Chronic lung disease	3 (4.68)
Cerebrovascular diseases	3 (4.68)
Solid organ transplant	3 (4.68)
Charlson comorbidity index (mean ± SD)	3.39 ± 3.22
Potential risk factors (last 90 days)	
Recent hospitalization	29 (45.31)
Recent surgical procedure	19 (29.68)
Stone former	14 (21.87)
On mechanical ventilation	13 (20.31)
Recent travel	5 (7.81)
Recent trauma	3 (4.68)
Presenting symptoms	
Fever	46 (71.87)
Respiratory symptoms	22 (34.37)
Urinary symptoms	19 (29.68)
Gastroenterology symptoms	15 (23.43)
Neurological symptoms	7 (10.9)
Others	13 (20.31)
Infection site	
Urinary tract	28 (43.75)
Respiratory system	19 (29.68
Blood (uncertain source)	7 (10.93)
Skin and soft tissue	5 (7.81)
Intra-abdominal	3 (4.68)
Implantable cardioverter-defibrillator	1 (1.56)
Eye	1 (1.56)
Bacteremia	17 (26.56)

(86%, 54/63), and levofloxacin (75% 40/53). High-level resistance was demonstrated for ertapenem (100%), cefepime (100%), gentamycin (98%), and piperacillin-tazobactam (68%) Table 3.

Discussion

BCc is a ubiquitous Gram-negative bacterium that is widely distributed in the environment causing both plant and animal diseases. The pathogen was first described by Walter Burkholder; a plant pathologist in the USA as the cause of decomposition of onion during the late 1940s and was eventually linked to human diseases in subsequent decades, particularly to the described aggressive form of respiratory diseases in patients with CF [2]. As opportunistic human pathogens, the Bcc family has a range of over 20 different sub-species dominated by *B. cenocepacia, B. multivorans,* and *B. veitnamesis* that are difficult to accurately sub-type since they share almost 80 % homology of identical genetic material but differ mainly in pathogenicity [2,13,14]. In addition, to the historic association with CF, the spectrum of Bcc opportunistic diseases has been linked usually to patients with underlying significant conditions such as vital organs dysfunctions, neoplastic and immune-compromised states usually associated with significant management challenges because of mounting virulence and antimicrobial resistance [15,16].

From our study, the first observation was that the disease is rare and infrequent in non-CF adult patients in the country since in 7 years period only 64 clinically relevant episodes were recorded with incidence ranging between 0.3-0.55 per 100.000 population Figure 1. Other related studies similarly recorded low incidence in non-CF adults [4,15]. Additionally, the fact that males are affected more than females has been previously observed but this can be explained locally by the country's diverse young population with male preponderance as outlined in Table 1 [16]. Likewise, the majority of patients were from Middle Eastern and Indian subcontinent populations in line with the country's established migration demographics [17]. Inversely, middle-aged patients are the most commonly affected group among the cohort explained by the observed associated chronic organ dysfunctions and neoplastic diseases as well as immune-compromised states in more than half of the cohort. Additionally, almost 40% of isolates were related to critical care where ultimate Bcc acquisition risks have been previously observed, furthermore, almost one-quarter of patients suffering from septic shock and 7% were undergoing hemodialysis which is fre-

Table 2
Management and outcomes.

Antibiotic	N (%)	Duration (mean ± SD)	
Meropenem	32 (50)	14.46±13.86	
Ceftazidime	24 (37.5)	15±9.3	
Cotrimoxazole	24 (37.5)	16.58±13.36	
Piperacillin/tazobactam	16 (25)	10.06±12.53	
Ceftriaxone	15 (23.43)	8.66±14.82	
Ertapenem	8 (12.5)	17.25±16.29	
Ciprofloxacin	7 (10.93)	9.57±6.2	
Levofloxacin	7 (10.93)	25.71±28.51	
Cefuroxime	6 (9.37)	6.83±3.48	
Tigecycline	5 (7.81)	16.4±7.81	
Moxifloxacin	4 (6.25)	15.5±8.2	
Gentamicin	2 (3.12)	11±8	
Cefixime	2 (3.12)	9±1	
Cefepime	1 (1.56)	19	
Polymyxin B	1 (1.56)	7	
Combined therapy	N (%)	Monotherapy	N (%)
MEM + TMP-SMX	7 (10.93)	Cotrimoxazole	8 (12.5)
CFZ + MEM	3 (4.68)	Meropenem	7 (10.93)
CFZ + MEM + TMP-SMX	2 (3.12)	Ceftazidime	6 (9.37)
CFZ + TMP-SMX	2 (3.12)	Ciprofloxacin	4 (6.25)
CFZ + LFX	2(3.12)	Ceftriaxone	3 (4.68)
Outcome			
Intensive care unit admission/mechanical ventilation/septic shock	60 (93.75)		
Complete resolution of symptoms	58 (90.62)		
Microbiological clearance	39 (60.93)		
Acute kidney injury/hemodialysis	22 (34.37)		
Recurrence/relapse	7 (10.93)		
30 days mortality	5 (7.81)		

CFZ, ceftazidime; MEM, meropenem; LFX, levofloxacin; TMP-SMX, cotrimoxazole.

Table 3
Microbiological characteristics.

Antibiotic	N out of 64	Sensitive N (%)	Intermediate N (%)	Resistant N (%)
Ceftazidime	63	54 (85.71)	2(3.17)	7(11.11)
Cotrimoxazole	63	59 (93.65)	0(0)	4 (6.34)
Gentamicin	62	1 (1.61)	0(0)	61 (98.38)
Amikacin	61	3 (4.91)	2 (3.27)	56 (91.8)
Ciprofloxacin	60	2 (3.33)	2 (3.33)	56 (93.33)
Aztreonam	57	11 (19.29)	8 (14)	38 (66.66)
Imipenem	57	4 (7)	8 (14)	45 (78.94)
Levofloxacin	53	40 (75.47)	7 (13.2)	6 (11.32)
Ceftriaxone	53	19 (35.84)	5 (9.43)	29 (54.71)
Ertapenem	45	0(0)	0(0)	45 (100)
Piperacillin/tazobactam	37	11 (29.72)	1 (2.7)	25 (67.56)
Cefuroxime	35	0(0)	0(0)	35 (100)
Cefepime	34	0(0)	0(0)	34 (100)
clindamycin	34	1 (2.94)	0(0)	33 (97)
Ampicillin	34	0(0)	0(0)	34 (100)
Amoxicillin	33	0(0)	0(0)	33 (100)
Tigecycline	31	1 (3.22)	0(0)	30 (96.77)
Meropenem	28	26 (92.85)	1 (3.57)	1 (3.57)
polymyxin B	1	1(100)	-	-

quently seen during critical care settings pointing toward acquisition through HCAIs [10]. To emphasize HCAIs as the main mode of acquisition of Bcc particularly in BSIs, in almost half of the examined cohort, recent hospitalization was evident and in almost one-quarter of the cohort, coinfection with other related organisms has been recorded predominated with Gram-negative bacteria Table 2. When examining infected sites, the most identified were the urinary and respiratory tracts followed by BSIs which is in line with other surveillance studies [16]. This can be explained by pathogen factors since the family of Bcc has specific virulence factors exhibiting predilection for the moist environment with motile and adhesion molecules that facilitate attachments to extracellular matrixes in the urinary and respiratory tracts while the invasive disease has been associated with biofilm formation around catheters, endotracheal tubes, and central venous lines which are frequent risk factors in hospitalized patients and critical care setting [14,16,18,19].

In addition to the described HCAIs, it is important to highlight that Bcc has been frequently associated with nosocomial outbreaks in different regions around the world particularly in critical care settings affecting vulnerable patients who undergo invasive procedures frequently linked to medication vials, disinfectants, and antiseptics [20]. Repeated, unusual patterns or clustering of isolated Bcc from clinically relevant isolates or sites should prompt early interventions to evaluate the scale of the problem to promptly establish needed infection and control precautions as well as expand surveillance concepts including phenotypic and genotypic methods [10,20-22]. In our cohort, the paucity and non-clustering of cases negate potential previous nosocomial bacterial outbreaks Table 2.

Being a well-known notoriously resistant pathogen, it was not surprising to notice that microbiological characteristics of Bcc revealed that multidrug-resistant isolates were observed in almost 90% of isolates with noticeable resistance to all major classes including advanced antimicrobials such as aminoglycosides, quinolones and specific BLBLIs such as piperacillin-tazobactam Table 3. In line with other related studies, antimicrobials that demonstrated the highest antimicrobial susceptibilities included cotrimoxazole (94%), meropenem (93%), ceftazidime (86%), and quinolones (levofloxacin 75%), but from previous studies, there were non-superiority of single or multiple regimens for effective management leading to frequently delayed clearance and recurrence rates as noticed in our study [15,16].

This established phenotypic pattern in Bcc is related to the inherited multifactorial mechanism of antimicrobial resistance since they possess unique lipopolysaccharide cell walls as well arrays of cytoplasmic or nuclear inactivating or modifying enzymes that are capable of inactivating multiple classes of antimicrobials simultaneously [5,9]. Consequently, infected patients were treated with multiple regimens leading to prolonged hospital stays averaging 24 days (range 8-50) which is similar to other clinical outcome studies Table 2 [15,16]. Since there are no specific guidelines for the treatment of Bcc in adults without CF, the usual approach is to rely on previously similarly described case studies and experts' advice to manage specific site infections sometimes with suboptimal outcomes [23,24]. These highlighted management challenges, particularly for respiratory-related diseases, led to consider novel and non-conventional approaches for disease control such as bacteriophage therapy that infect, commandeer, and destroy target pathogens either as sole therapeutic agents or in combination with synergistic antimicrobials [25,26].

Distinctively our study showed lower 30-day mortality rates at 7.8% when compared to other studies which recorded rates as high as 50% [10,26]. To explain that in comparison to other studies, we can speculate dominance or scatter of low virulent clones as well as the absence of recorded outbreaks [4,26–28]. From previous research, highly virulent clones are associated with outbreaks with increased morbidity and mortality but faced with accurate typing methods which limits its frequent use [15,16,26,29,30].

Although the study covered many epidemiological, clinical, and microbiological aspects of the challenging disease secretum, it has some limitations. The retrospective study design certainly affected the quality of obtained data since additional details for invasive diseases such as BSI could have been closely examined but such an approach can be justified by the rarity of the studied subject. Furthermore, since *Burkholderia species* need special slecetive media for proper identification and its ASTs are cumbersome , routine microbiologicalcharacteristics were not uniform for all isolates to make accurate comparisons and lastly, the lack of genomic testing would have added additional strength to accurately examine sub-species in more detail together with pathogenicity and clonal relatedness. Nevertheless, because of the complexity of the pathogen, routine microbiological and genomic tests are not accurately reliable or uniform [4].

In conclusion, our study of *Burkholderia* species in Qatar over 7 years focusing on Bcc demonstrated infrequent but prominent challenges manifesting mainly as isolated respiratory, urinary, or BSIs with a noticeable antimicrobial resistance spanning all classes leading to the use of multiple antimicrobial regimens, associated with prolonged length of hospital stay and low 30-day mortality.

Declarations of competing interest

The authors have no competing interests to declare.

Funding and approval

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Author contributions

TI and HAH conceived and designed the study. TI, TA, AA, RQ, HM, and FE collected clinical and microbiological data while TI and JD analyzed the results. TI and HAH drafted the initial manuscript. TA, AA, and MA reviewed and edited the manuscript toward the final draft. All authors read and approved the final manuscript.

Consent for publication

All authors reviewed and agreed on the final manuscript and consent for its publication.

Availability of data and material

Confidence was maintained during data collection and processing throughout the study. Non-authorized access to the data was prohibited except for primary investigators. Availability of data is possible upon a reasonable request to the authors following permission from the Medical Research Centre.

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