Epidemiology and outcomes of *Stenotrophomonas maltophilia* and *Burkholderia cepacia* infections among trauma patients of India: a five year experience

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Abstract

Background: Infections by uncommon non-fermenting Gram negative bacteria are on the rise, but little is known about the risk factors and drug resistance in trauma patients in India. This study explored the infections caused by *Stenotrophomonas maltophilia* and/or *Burkholderia cepacia* in trauma patients over a period of 5 years.

Material and methods: Patients admitted for trauma care with *S. maltophilia* and/or *B. cepacia* isolated from clinical specimens were enrolled. Characteristics regarding the strain isolation, drug sensitivity pattern, multidrug resistance (MDR), patient, outcomes, and differentiation of true infection from colonisation were observed.

Results: Of the total 233 isolates, 102 were *S. maltophilia* and 131 were *B. cepacia*; 4.3% were responsible for polymicrobial infections with other bacteria. There were more *B. cepacia* MDR isolates than *S. maltophilia*. Maximum resistance was found to tetracycline (86.7%) and tobramycin (86.7%) in *B. cepacia* and to co-trimoxazole (68.7%) in *S. maltophilia*. Of these, 21 (16.03%) had a fatal outcome and the remaining 111 (84.7%) were discharged healthy. The in-hospital mortality rate associated with *B. cepacia* was much (16%) higher than *S. maltophilia* (13%) at this centre.

Conclusion: The analysis of epidemiology and outcome of these infections will help to inform their management and treatment.

Keywords

Bacteria, epidemiology, infection, infection prevention and control, surveillance

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Introduction

As infections due to non-fermenting Gram negative bacteria (NFGNB) are on the rise in nosocomial settings, it is important to study their epidemiology. Unlike the well-known *Acinetobacter baumannii* and *Pseudomonas* spp., infections due to other non-fermenting bacteria, such as *Burkholderia* spp. and *Stenotrophomonas maltophilia*, are steadily increasing. The emergence of new multidrug-resistant (MDR) organisms (MDROs) found in nonclinical environments, the increasing reports of community acquired

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infections, and the spread of these pathogens in the clinical setting all underscore the need to monitor these organisms. The increase in reported cases of MDRO associated infections has resulted in efforts to examine the possible sources of these pathogens and assess the current antimicrobial strategies used for the treatment of infections (Brooke, 2012).

Stenotrophomonas maltophilia is an environmental pathogen that is ubiquitously distributed and usually associated with respiratory infections in humans (Brooke, 2012). The incidence of infection due to *Burkholderia* spp. is also on the rise, even in non-cystic fibrosis patients (Takigawa et al, 1993). As the knowledge of infections caused by these uncommon NFGNB is limited, especially in trauma patients and developing nations, it is essential to estimate the magnitude of infectious burden due to these pathogens. Therefore, we conducted this retrospective observational study to analyse the epidemiology of infections caused by *S. maltophilia* and *B. cepacia* in an acute trauma care facility and to measure the baseline antibiotic resistance pattern and outcomes in these trauma patients.

Material and methods

Settings

This retrospective study was conducted from January 2008 to February 2013 at a level I trauma centre in India. Our trauma centre is a well equipped Level I trauma care facility which has 176 functional beds out of a total of 186 beds, with an average total admissions per year of 4,094 during the study period. The hospital bed occupancy rate was 83% with an average bed turnover rate per day of 24. A total of 50,137 emergency visits and 4,384 major surgical procedures were performed out of a total of 4,850 surgical procedures during the study period per year. The length of hospital stay of the trauma patients ranges from 7–15 days unless they require extended stay due to their condition. All patients who had been admitted for trauma care during the study period and who at one time had had positive culture with *S. maltophilia* and/or *B. cepacia* were included in the analysis, irrespective of the type of sample. Information such as age, sex, previous hospitalisation, use of antimicrobial therapy, length of hospital stay and interventions performed, were noted from the hospital information system. The findings regarding their underlying conditions, any change in treatment regime and their eventual outcome were also noted where possible. Details were also noted about the patients' other bacterial isolates and, if available, the condition of the patient at the time of discharge. If the same NFGNB was isolated on multiple occasions from the same patient, only the first episode was included to avoid duplication of patients.

Microbiological procedure and isolate identification

All the microbiological samples were sent as a part of routine diagnostic procedure or if any specific tests were required by the treating team. If needed, repeat samples were requested by the microbiologists' team for confirmation. Microbiological culture report and susceptibility pattern of the isolates from all patients showing positive culture with either *S. maltophilia* and/or *B. cepacia* were obtained from the hospital database, together with co-infection with other bacteria. All samples were processed in the laboratory as per standard microbiological procedures (Collee et al, 1996). For the blood cultures, all samples were processed using the Bact T/ALERT system (bioMérieux, Lyon, France) according to the manufacturer's protocol. Identification to the species level and antimicrobial sensitivity was done using the VITEK 2 Compact system (bioMérieux, Durham, US). Sensitivity tests using Kirby-Bauer's method were also done in parallel according to the CLSI guidelines (CLSI, 2010a,b, 2012).

MDR was defined as resistance to carbapenems, second and third generation cephalosporins, anti-pseudomonas penicillins, fluoroquinolones and aminoglycosides (Rattanaumpawan et al, 2013). The site of infection was defined using the Centers for Disease Control and Prevention (CDC) definition of nosocomial infections (Garner et al, 1988; Horan et al, 2008). The CDC has developed a new set of definitions for surveillance of nosocomial infections. The new definitions combine specific clinical findings with results of laboratory and other tests that include recent advances in diagnostic technology; they are formulated as algorithms (Garner et al, 1988; Horan et al, 2008). Under our hospital policy, an empiric regime was started on trauma patients are considered to potentially have an infection and later shifted to a more specific regime depending on the micro-organism isolated and its sensitivity report. Empiric therapy was usually started with parenteral augmentin (amoxicillin-clavulanic) along with aminoglycosides and/or metronidazole. However, aminoglycosides were used cautiously or avoided in very severe trauma patients due to their potential nephrotoxicity in a hypovolemic patient at risk of renal insufficiency.

Statistical analysis

Descriptive statistics were used in expressing overall results. Categorical variables were compared by using Fisher's exact test or χ^2 statistics, while continuous variables were compared using Student *t*-test. A *p*-value of <0.05 was considered significant. All statistical analysis were done using SPSS software version 17 for Windows (SPSS Inc. Chicago, IL, version 17.0).

Ethical approval was obtained from the institute's ethical committee for accessing the data from the hospital database for the study.

Table 1. Patient characteristics and clinical features of the patients with *Burkholderia cepacia* group vs. those with *Stenotrophomonas maltophilia*.

Variables	<i>Burkholderia cepacia</i> (n=131)	<i>Stenotrophomonas maltophilia</i> (n=102)	p-value
Median age	42 (2–82)	38 (1–75)	–
Median length of hospital stay	235 (45–424)	228 (60–396)	–
Male sex	111 (84.7%)	74 (77.15)	0.143
Wards			0.033
Surgery ICU	50 (38.2%)	37 (39.5%)	
Neurosurgery ICU	41 (31.1%)	23 (24.4%)	
Orthopaedic ICU	4 (3.1%)	13 (13.5%)	
Surgery ward	7 (5.3%)	3 (3.1%)	
Neurosurgery ward	26 (19.8%)	14 (14.6%)	
Orthopaedic ward	2 (1.5%)	2 (2.1%)	
OPD/Emergency	1 (0.8%)	4 (4.2%)	
Samples			0.241
Blood	49 (38.0%)	45 (46.9%)	
Bronchoalveolar lavage fluid	21 (16.3%)	12 (12.5%)	
Tracheal aspirate	35 (27.1%)	29 (30.2%)	
Urine	4 (3.1%)	0 (0.0%)	
Pus/wound swabs	13 (10.1%)	6 (6.3%)	
Fluids	5 (3.9%)	1 (1.0%)	
CVP tips	2 (1.6%)	3 (3.1%)	
Clinical features			0.009
Fever	65 (47.1%)	49 (46.7%)	
Septicaemia	9 (6.5%)	13 (12.4%)	
Multiple fracture	16 (11.6%)	10 (9.5%)	
Head injury	5 (3.6%)	8 (7.6%)	
Patient on ventilator	8 (5.8%)	13 (12.4%)	
Chest injury with pleural effusion	12 (8.7%)	3 (2.9%)	
Abdominal injury	6 (4.3%)	5 (4.8%)	
Others	17 (12.3%)	4 (3.8%)	

Results

Patient characteristics

The details regarding the median age, gender, wards, median length of hospital stay, clinical presentation and different microbiological samples sent are given in Table

1. Based on data from 233 non-duplicate patients, the median age (interquartile range) of our study subjects was 42 years (2–82) among the patients from whose samples *B. cepacia* was isolated and 38 years (1–75) among the patients whose samples yielded *S. maltophilia*. The median length of hospital stay was 235 days (45–424) and 228

Figure 1. Monthly distribution of *Burkholderia cepacia* and *Stenotrophomonas maltophilia* with the resistance pattern of the representative antibiotics of each group used in treating both organisms.

(*Shows the resistance pattern to both *B. cepacia* and *S. maltophilia*. No of each organism describes the total isolates in each month, whereas % in the antibiotic shows the resistance pattern of each organism in total month of all the years).

days (60–396) from patients with *B. cepacia* and *S. maltophilia*, respectively. Males (191, 82%) exceeded females (42, 18.0%) in terms of patient admission ($p=0.143$). Both *B. cepacia* (38.2%) and *S. maltophilia* (39.5%) were most commonly isolated from the surgery ward. Fever was the most common clinical feature followed by fever with septicemia. There was a history of previous hospitalisation in 48% (63) of the patients in whom *B. cepacia* was isolated and in 74% (75) from whom *S. maltophilia* was isolated. Of the total, 51 patients had a history of two admissions to the hospital.

Distribution of causative pathogens

During the study period, a total of 62,019 different clinical samples were analysed by microbiological testing, out of which 30,812 gave positive culture, irrespective of the type of organism. From the total 30,812 positive cultures, 21,115 isolated different types of Gram negative bacteria. Of the total Gram negative bacteria, 131 isolates were of *B. cepacia* and 102 were new isolates of *S. maltophilia*. Of these, 10 (4.3%) samples also yielded a pathogen apart

from *S. maltophilia* and/or *B. cepacia*. Co-isolation of *B. cepacia* and also *S. maltophilia* with other organisms were seen. The most common combination was *B. cepacia* and *Klebsiella pneumoniae* ($n=2$) and *S. maltophilia* with *A. baumannii* ($n=2$). It was seen that *S. maltophilia* and/or *B. cepacia* isolation was more likely to occur after hospitalisation of two weeks but polymicrobial infections were more likely to occur after one month of hospital stay. Infection with either of these bacteria was more likely one to two weeks after respiratory manipulation or surgery.

The maximum number of isolates of *B. cepacia* was obtained during December (21, 16%), and during November (19, 18.6%) in *S. maltophilia*. The month-wise distribution and yearly variation are given in Figure 1 and Figure 2, respectively.

Antimicrobial susceptibility of *Stenotrophomonas* spp. and *Burkholderia* spp.

The details of the sensitivity pattern are described in Table 2. The prevalence of MDR in *B. cepacia* was higher

Figure 2. Distribution of antimicrobial sensitivity and trend during the study period (2008–2013).

(*Shows the resistance pattern to both *B. cepacia* and *S. maltophilia*. No of each organism describes the total isolates in each year, whereas % in the antibiotic shows the resistance pattern of each organism in each year of the study period).

compared to that of *S. maltophilia*. Of these, maximum resistance was found to tetracycline (86.7%) and tobramycin (86.7%) in *B. cepacia* and to co-trimoxazole (68.7%) in *S. maltophilia*. The monthly and yearly trend of antibiotic sensitivity was also analysed for both the micro-organisms and is shown in Figure 1 and Figure 2, respectively.

Clinical outcomes

A total of 131 non-duplicate patients had *B. cepacia* isolated from various clinical samples. Twenty-one (16.03%) had a fatal outcome and the remaining 110 (83.9%) were discharged as healthy after treatment. Similarly, among the 102 patients whose samples had *S. maltophilia*, 10 (9.8%) patients died and the remaining 92 (90.2%) had their treatment reviewed and were later discharged as healthy. Thus, a total of 31 (13.3%) patients had fatal outcome during the study period ($p=0.172$). The mortality associated with *B. cepacia* was much more than that with *S. maltophilia* at our centre. In the fatal cases, infection with either of the organisms contributed to mortality. The rate of infection caused by both these organisms was 1.1%, taking

20,470 as the total admissions during the study period. However, the rate of infection due to *B. cepacia* was 0.63% and that due to *S. maltophilia* was 0.49%. The infection caused by monomicrobial infections either by *B. cepacia* or *S. maltophilia* outnumbered those caused by polymicrobial infections. Also, septicaemia was the most common presentation in patients infected with *B. cepacia* whereas ventilator associated pneumonia was the most common condition associated in those patients fatally infected with *S. maltophilia*.

Discussion

In our study, *B. cepacia* was observed to exceed *S. maltophilia* in causing infections in trauma patients. Isolation in male patients outnumbered female patients, which might reflect the preponderance of male patients in terms of admission. These pathogens are ubiquitous, opportunistic agents causing infections during long-term hospital stay. In a study by Wood et al (2005) *S. maltophilia* caused 9–12% of late onset (7 days) ventilator associated pneumonia in their study in the ICU of a regional trauma center. In our

Table 2. Antibiotic sensitivity pattern of *Burkholderia cepacia* and *Stenotrophomonas maltophilia* during the 5 year study period.

Antimicrobial agents	<i>Burkholderia cepacia</i>			<i>Stenotrophomonas maltophilia</i>			p-value
	R	S	I	R	S	I	
Ceftazidime	51.8 (43/83)	44.6 (37/83)	3.6 (3/83)	21.2 (21/99)	78.8 (78/99)	0	<0.001
Cefepime	51.8 (43/83)	41 (34/83)	7.2 (6/83)	–		–	
Imipenem	73.5 (61/83)	25.3 (21/83)	1.2 (1/83)	–		–	
Meropenem	42.2 (35/83)	53 (44/83)	4.8 (4/83)	–		–	
Tobramycin	86.7 (72/83)	12 (10/83)	1.2 (1/83)	–		–	
Co-trimoxazole	50.6 (42/83)	42.2 (35/83)	7.2 (6/83)	68.7 (68/99)	31.3 (31/99)	0	0.004
Tetracycline	86.7 (72/83)	12 (10/83)	1.2 (1/83)	–		–	

R=resistant, S=sensitive, I=intermediate.

% resistant (no. of resistant isolates/total no. of isolates tested).

% sensitive (no. of sensitive isolates/total no. of isolates tested).

% intermediate (no. of intermediate isolates/ total no. of isolates tested).

study, *S. maltophilia* accounted for 43.8% (102), of the isolates but over 80% of patients improved just from the removal of any indwelling catheter or instrument, and the remainder either improved after a change of therapy or had a fatal outcome. However, in the 131 case of *B. cepacia*, 78% had to undergo revision of therapy or required a combination of oral and parenteral therapy. In our centre, *B. cepacia* is the major species of *Burkholderia* in the pathogenic group, and therefore we have only analysed the data for *B. cepacia*.

It was seen that 51 patients had two admissions to the hospital and this might also reflect the acquisition of colonisation by these pathogens. Also, 70% of the isolates from these patients with multiple admissions were found to be MDR strains, indicating the acquisition of hospital strains which are usually MDR. This pattern also depends on the length of hospital stay of these patients. It was seen that MDR isolation of either *B. cepacia* and/or *S. maltophilia* increases in those patients who had hospital stay of 14 days or more. This indicates that longer duration might be responsible for the patients getting infected with either of the bacteria in otherwise healthy trauma patients. This finding is in contrast to another study which showed that there is no association between the length of hospitalisation and length of exposure to the hospital environment with the risk of *B. cepacia* acquisition in cystic fibrosis patients (Shreve et al, 1997). All these factors may act as risk factors to infections with *B. cepacia* and/or *S. maltophilia* in trauma patients admitted to long-term health-care facilities. The use of an automated data entry system for hospital infection surveillance helped us in studying the clinical outcomes of the patients.

Although fever was the most common manifestation in patients infected with either of the organisms, other most

commonly observed clinical presentations in patients infected with *B. cepacia* were multiple fractures and chest injuries with pleural effusion, whereas septicaemia and assisted ventilation were seen in a majority of patients infected with *S. maltophilia*. These might be a predisposing factor in infections caused by either of these organisms in trauma patients who had been hospitalised for a long duration, although this needs further investigation.

Ceftazidime and co-trimoxazole given alone or in combination have been recommended as a treatment of choice for *S. maltophilia* infection (Wang et al, 2013). According to our susceptibility results, however, ceftazidime appeared to be the most promising therapeutic option rather than co-trimoxazole that others have suggested to be the ideal agent for therapy (Rattanaumpawan et al, 2013).

Infections caused by *B. cepacia* are usually treated by ceftazidime or carbapenems (Yildiz et al, 2012). Co-trimoxazole is documented as the best oral eradication-phase therapy regardless of the susceptibility result. However, in our study, meropenem showed 53% sensitivity, whereas ceftazidime, co-trimoxazole and imipenem showed only 44.6%, 42.2% and 25.3% sensitivity, respectively. Thus, carbapenems were used mostly in the treatment of infections due to *B. cepacia* in our setup. Our study tried to explore the resistance pattern and treatment of these two organisms in different samples from all trauma patients. Improvement in, proper antibiotic stewardship is needed to be to prevent the development of multidrug resistant strains, including proper control of the empiric therapy documentation of antibiotic prescription and prescription only when needed. The antimicrobial therapy needed to be continued for two to three weeks in *B. cepacia* infections and one to two weeks in those with *S. maltophilia* infections in our

study. This duration may depend on the nature of the causative organism, which was also observed in another study (Magnotti et al, 2011). Prior hospital admission may also be an increased risk factor for development of infection in such patients, and this needs to be documented.

The mortality rate was higher in patients with *B. cepacia* infections (16.03%) compared to those caused by *S. maltophilia* (9.8%). This may be due to the fact that even though *S. maltophilia* is a highly drug resistant organism, many patients improved after the removal of any catheters/instruments or revision of therapy, which was not seen with *B. cepacia*. It was seen that 5.2% of the patients who died had *B. cepacia* infection alone whereas the remainder died due to the complications of trauma along with infections. On the contrary, 2.6% of the patients died because of infection by *S. maltophilia*, whereas the remainder died due to a combination of trauma and infections. However, the mortality reflects the crude rate only. There may have been other trauma-related factors accounting for the fatal outcome that we could not study.

There was no definite seasonal variation of the isolation of either organisms, but their isolation is more common during the high influx of patients, especially when they require long-term hospital stay. However, in the year-wise distribution, *B. cepacia* infections were higher at the start of the study (2008) and slowly declined (2010), followed by an increase in 2012–13. The reverse pattern was seen in the case of *S. maltophilia*. A literature review shows that no study has elucidated the seasonal trends of these pathogens.

Our study has several strengths. First, it focused mainly on *B. cepacia* and *S. maltophilia* infections in trauma patients, a population largely devoid of other medical comorbidities, whereas most reported studies have focused on patients with cystic fibrosis (Spicuzza et al, 2009; Waters et al, 2013; Correa-Ruiz et al, 2013). Second, our study attempted to distinguish those with true infections based on CDC definition and not just mere colonisation, whereas other studies failed to differentiate true infections from colonisation (Vidal et al, 2003). Third, monthly and yearly distributions of these two bacteria along with antibiotic resistance patterns were observed, compared and analysed. As a result of this study, a protocol on the duration of the use of indwelling devices has been implemented. Avoidance of unnecessary devices and catheters and the use of proper antimicrobial stewardship should be in place.

The study was not without limitations. First, most of the data were retrospectively obtained and certain data regarding the patients' exact therapeutic interventions could not be obtained. We could not ascertain the attributable mortality due to these pathogens. Molecular mechanisms of resistance could also not be ascertained.

Conclusion

The epidemiology of *B. cepacia* and *S. maltophilia* in our trauma centre differed from that prevalent in other hospitals

and from other previous studies. The mortality rate of infections caused by *B. cepacia* was higher than those caused by *S. maltophilia*. There is a strong need to properly differentiate colonisation from true infections. Although a high rate of MDR is prevalent in our hospital, antimicrobial agents are still available to treat these infections.

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Declaration of conflicting interests

The authors state that they have no conflict of interest.

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