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Extended spectrum beta lactamases producing non-lactose fermentative bacterial isolates causing blood stream infections in children

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Abstract

Blood stream infections (BSIs) are the important cause of morbidity and mortality in pediatrics. BSIs are usually caused by common gram positive and gram negative bacterial isolates but few uncommon bacteria may lead to BSIs in children significantly. The aim of the present study was to determine the drug resistance pattern of uncommon non-lactose fermenting gram negative bacterial isolates from blood specimen of children. A cross sectional study was conducted at tertiary care hospital, Peshawar from June to December 2018. Blood specimens were collected aseptically in BACTAM™ bottles and were processed in BACTEC 9120 according to the standard protocol. Antibiotics resistance profile was determined by using Kirby-Bauer Disc diffusion method. Bacterial isolates showed resistance to cephalosporin were further verified for extended spectrum beta lactamases (ESBL) by double disc diffusion method according to the clinical laboratory standards institute guidelines. Out of total, 20.6% were positive with significant growth in which 6.0% (07) isolates were non-lactose fermenter gram negative bacteria including *Morgenella morganii* (0.9%), *Stenotrophomonas maltophila* (2.7%), *Acinetobacter baumannii* (0.9) and *Burkholderia cepacia* (1.8%). Colistin/Polymixin B was found only effective antibiotics against *Acinetobacter baumannii*. Among recovered isolates, 42.9% were ESBL producer while 71.4 % were found multidrug resistant strains. It is concluded that non-fermenter bacterial isolates can contribute in blood stream infections significantly. ESBL producing by non-lactose fermenter bacterial isolates were identified with emerging MDR isolates to various antibiotics classes which is major concern in developing countries.

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Introduction

A blood stream infection (BSIs) is the most important cause of high mortality and morbidity, frequently associated with health care infections (Kotgire and Hathkar, 2017). Blood stream infections are responsible for about 20-50% mortality rate (Barati*et al.,* 2009). Presence of bacteria in the blood stream is considered bacteremia (Peterside *et al.,* 2015). Bacteremia is the life threatening situation for every part of the body (Kotgire and Hathkar, 2017). BSIs may lead to serious consequences including the shock, multi organ failure and disseminated intravascular coagulation and even death (Banik *et al.,* 2018).

BSIs are frequently caused by bacteria such as *Salmonella* species, *E. coli*, *Staphylococcus aureus*, *Pseudomonas aeruginusa*, *Klebsiella pneumonia*, *Proteus* species (spp.) and *Enterococcus* spp 33. Besides these bacteria, few uncommon bacteria may lead to cause BSIs including *Stenotrophomonas maltophilia, Acinetobacter baumannii, Burkholderia cepacia* and *Morganella morganii* (Barati *et al.,* 2009). These bacteria have less importance in community but considered as important nosocomial pathogens, which may cause septicemia, meningitis, urocystitis, endocarditis, pneumonia and lesions infection especially in children and other immunocompromised patients (Montefour*et al.,* 2008; Laing *et al.,* 1995).

These uncommon bacteria are reported in children and infants (Muneeza *et al.,* 2016). In the previous five decades, non-fermentative gram negative isolates appear as a crucial health care associated bacteria due to the widely use of antibiotics.

These pathogens spread through environmental surfaces and direct contact with health care workers between infected patients and healthy individuals. These non-fermenter bacterial isolates are usually present as a normal flora of human intestine. It is responsible for causing diseases in neonates and post operation phase typically in diabetic individuals (McDonald *et al.,* 1999).

Antimicrobial resistance is growing worldwide due to misuse and empirical therapy. Irrational use of antibiotics has led to increased resistance and lead to multidrug resistant pattern and thus worsened the situation. Globally, about 31% neonatal death occurs every year due to multi-drug resistant (MDR) isolates (Laxminarayan *et al.,* 2016). High level of MDR strain increased the risk of infection along with mortality rate among children (Van Nguyen *et al.,* 2016).

Microbial pattern of non-fermenter bacteria and their susceptibility pattern of these bacteria are important to observe time to time, due to varying the geographical variation with the passage of time.

Therefore, it is important to know the microbial pattern particularly the hidden non-lactose fermenter microorganism causing life threatening infections in human. Limited or no data are available of these uncommon bacterial isolates and their antibiotics resistance pattern in our community.

Thus, current study was undertaken to evaluate the non-fermenter bacterial isolates (*Morganella morganii, Stenotrophomonas maltophilia, Acinetobacter baumannii* and *Burkholderia cepacia*) causing BSIs and their antibiotics resistance profile for appropriate management of these infections.

Methodology

Study design, duration and setting

This descriptive cross-sectional study was conducted in the Department of Microbiology, Khyber Teaching Hospital Peshawar, Pakistan from June to December 2018.

Sample size, inclusion and exclusion criteria

A total of 567 blood samples were collected from children suspected for BSIs before the start of antimicrobial therapy. Patients with incomplete medical records and repeated samples were excluded.

Study approval

The study was conducted after the approval from hospital concern authority.

Procedure

The blood specimens (1-5 ml) were collected aseptically from each suspected patients and inoculated in BACTEC™ culture bottles. All BACTEC™ blood culture bottles were loaded aerobically for seven consecutive days at 37°C on automatic blood culture system "BD BACTEC™ (Automatic Machine Model: 9120") (Becton Dickinsin Spark, Maryland). During the incubation periods, microbial growth could be detected by flag and audible sound (positive) on automated BACTEC™ instrument and that samples were withdrawn; then about 3-5 drops of the positive blood sample were inoculated after gentle shaking on blood agar (containing 5% sheep blood) and MacConkey's agar and incubated for 18-24 hours for 37°C for bacterial growth culture. A smear was prepared for gram staining according to the standard protocol. All petri plates were observed for the growth, isolation and identification of positive bacterial culture from subculture samples on their respective media. Speciation of the isolates was confirmed by using pattern of conventional biochemical and using analytical profile index 20-E strips with standard guidelines (LQAPM, 2016).

Antimicrobial susceptibility testing

Antimicrobial susceptibility testing of bacterial isolates was performed by using Kirby-Bauer disk diffusion method in accordance with Clinical Laboratory Standard Institution (CLSI) recommendations (CLSI, 2014). Gram negative bacteria were identified by analytical profile index (API20E) identification strips (Oxoid Ltd. England). The antimicrobial disks (Oxoid Ltd. England) used for bacterial isolates were following: aztreonam (30ug), tazocin: piperacillin/tazobactam (40ug), meropenam (10ug), levofloxacin (05ug), ciprofloxacin (05ug), ceftriaxone (30ug), ampicillin (10ug), ampicillin/sulbactam (10ug), cefipime (30ug), cefaperazone/sulbactam (30ug), cefotaxime (30ug), colistin/polymixin B (10ug), co-trimoxazole: trimethoprim-sulphamethoxazole (25ug), doxycycline (30ug), gentamicin (10ug), amikacin (30 µg), ceftazidime (30 ug) and imipenem (10 µg). Standard inoculums of bacteria (Mcfarland Standard 0.5) was prepared by mixing of few colonies in 5.0 ml saline with 0.85% NaCl and swabbed on Muller-Hinton Agar (MHA) (Oxide Ltd. England); disc was dispense and incubated at 370C for 18-24 hours.

The standard strain of American Type Culture Collection (ATCC) was used as a reference strains such as *Escherchia coli* (ATCC 25922), *Staphylococcus aureus* (ATCC 25923) and *Pseudomonas aeruginusa* (ATTC 27853). CLSI guidelines were used for measurement and interpretation of the zone of inhibition.

MDR and ESBL

Multi-drug resistant strains were detected and were further processed for identification of phenotypic detection of extended spectrum beta lactamases (ESBL) bacterial isolates by double disk method (cephalosporins and aztreonam) (CLSI, 2014).

Data analysis

Statistical analysis was primary performed on Excel Spread Sheet (Microsoft Excel 2016) and further analyzed by Statistical Package for Social Sciences (SPSS) software, version 22 (IBM corp., USA).

Results

A total of 567 blood culture samples were collected from children, in which 20.6% (n=117) were culture positive with a significant bacterial growth whereas 79.4% (n=450) blood samples were yield no growth as shown in table 1.

Table 1. Frequency of bacteria causing blood stream infections in children.

Bacteria Frequency	Positive Culture	Negative Culture	Total
Number	117	450	567
Percentage	20.6%	79.4%	100%

Out of total, only 6.0% (n=07) samples were positive for non-lactose fermenter bacteria including *Morgenella morganii* (0.9%, n=01), *Stenotrophomonas maltophila* (02.7%, n=03), *Acinetobacter baumannii* (0.9%, n=01) and *Burkholderia cepacia* (01.8%, n=02) while the rest of 110 bacterial isolates were the common gram positive and gram negative bacterial isolates including *Salmonella* species, *E. coli*, *Enterobacter* species, *Staphylococcus aureus*, *Streptococcus* species and *Enterococcus* species as shown in table 2 and 3.

Table 2. Frequency of culture positive bacterial growth causing blood stream infections in children.

Bacteria Frequency	Non-Fermenter	Others	Total
Number	07	110	117
Percentage	6.0%	94.0%	100%

Non-Fermenter= *Morgenella morganii*, *Stenotrophomonas maltophila*, *Acinetobacter baumannii* and *Burkholderia cepacia*

Others= *Salmonella* species, *E. coli*, *Enterobacter* species, *Staphylococcus aureus*, *Streptococcus* species and *Enterococcus species*.

Antibiotic susceptibility pattern were observed for recovered bacterial isolates. *Morgenella morganii* showed resistance against certain antibiotics including ciprofloxacin and ampicillin (100% each) whereas various antibiotics were effective against *Morgenella morganii* such as aztreonam, amikacin, ceftriaxone, ceftazidime, cefipime, cefaperazone/sulbactam, gentamicin, imipenam, levofloxacin, meropenam and piperacillin/ tazobactam. *Stenotrophomonas maltophila* was 100% susceptible to imipenam and co-triamoxazole (n=3 each), followed by aztreonam, meropenam and piperacillin/tazobactam (66.7% sensitive each) and least sensitive antibiotics was ciprofloxacin, ceftriaxone, amikacin, gentamicin and cefipime (33.3% sensitive each).

Table 3. Non-fermenter gram negative bacteria causing blood stream infections in children.

Bacteria	*Morgenella morganii*	*Stenotrophomonas maltophila*	*Acinetobacter baumannii*	*Burkholderia cepacia*	Total
Number	01	03	01	02	07
Percentage	0.9%	2.7%	0.9%	1.8%	6.0%

On the other hand, non-effective antibiotics against *Stenotrophomonas maltophila* bacterial isolates were ampicillin only with 100% resistance. *Acinetobacter baumannii* was showed high resistance to all tested antibiotics except colistin/Polymixin B. *Burkholderia cepacia* was resistance to only co-triamoxazole while other effective antibiotics were also observed piperacillin/tazobactam and cefaperazone/sulbactam (100% sensitive each) as shown in Table 4.

Among the studied bacterial isolates, 42.9% (n=3) were ESBL producer in which highest percentage were found among *Acinetobacter baumannii* 100% (n=1), followed by *Burkholderia cepacia* 50% (n=1), *Stenotrophomonas maltophilia* 33.3% (n=1). No ESBL producer was found in isolates of *Morgenella morganii* as shown in Table 5.

Additionally, the recovered bacterial isolates from blood specimens were further processed for MDR. Out of total, 71.4% (n=5) isolates were resistant to three or more classes of antibiotics. Within species highest number of MDR strains were observed in *Acinetobacter baumanni* 100% (n=1) and *Burkholderia cepacia* 100% (n=2), followed by *Stenotrophomonas maltophilia* 66.7% (n=2) whereas no MDR were found in *Morgenella morganii* as shown in Table 6 and 7.

Table 4. Antibiotic resistance pattern of non-fermenter gram negative bacteria causing blood stream infections in children.

Antibiotics	*Morgenella morganii* (n=01)	*Stenotrophomonas maltophila* (n=03)	*Acinetobacter baumannii* (n=01)	*Burkholderia cepacia.* (n=02)	Total (n=07)
Aztreonam	0 (00)	01 (33.3)	NT	01 (50.0)	33.3%
Tazocin	0 (00)	01 (33.3)	1 (100)	0 (00)	28.8%
Meropenem	0 (00)	01 (33.3)	1 (100)	01 (50.0)	42.9%
Levofloxacin	0 (00)	NT	NT	01 (50.0)	33.3%
Imipenem	0 (00)	0 (00)	1 (100)	NT	20.0%
Gentamicin	0 (00)	02 (66.7)	1 (100)	01 (50.0)	57.1%
Ciprofloxacin	1 (100)	02 (66.7)	1 (100)	01 (50.0)	71.4%
Ceftriaxone	0 (00)	02 (66.7)	1 (100)	01 (50.0)	57.1%
Ampicillin	1 (100)	03 (100)	1 (100)	01 (50.0)	85.7%
Amikacin	0 (00)	02 (66.7)	1 (100)	01 (50.0)	57.1%
Ceftazidime	0 (00)	NT	1 (100)	01 (50.0)	50.0%
Cefipime	0 (00)	02 (66.7)	1 (100)	01 (50.0)	57.1%
Doxycycline	NT	NT	NT	01 (50.0)	50.0%
Cefaperazone/Sulbactam	0 (00)	NT	1 (100)	0 (00)	50.0%
Cefotaxime	NT	NT	1 (100)	NT	100%
Colistin/Polymixin B	NT	NT	0 (00)	NT	0.00%
Co-triamoxazole	NT	0 (00)	1 (100)	02 (100)	50.0%

NT= Not tested.

Discussion

A total of 567 blood samples were collected in which 20.4% were culture positive. Out of total positive culture blood samples, 6.0% samples were positive for non-fermenter bacteria which is nearly similar to study conducted at Lahore (Pakistan) by Naveed *et al.*, 2018, whereas comparatively low percentage had been reported by United State of American by Adams *et al.,* 2012.

Table 5. Distribution of ESBL producing non-fermenter gram negative bacteria causing blood stream infections in children.

Bacteria	ESBL n (%)		Total n (%)
	No	Yes	
Morganella morganii	01 (00)	00	01 (14.3)
Stenotrophomonas maltophilia	02 (66.7)	01 (33.3)	03 (42.9)
Acinetobacter baumannii	00	01 (100)	01 (14.3)
Burkholderia cepacia	01 (50.0)	01 (50.0)	02 (28.5)
Total	04 (57.1)	03 (42.9)	07 (100)

The low proportion of the yielded pathogens in the other studies could be due to the variation in detection techniques, inoculation of low blood in BACTEM™ bottles and management of BSIs before use of antibiotics. Individually, *Morgnella morganii* prevalence of present study was comparatively similarly to the previous study conducted at Pakistan and USA while high proportion were also reported from other regions of the world (Adams *et al.*, 2012; Ahmad *et al.*, 2012; Dimple *et al.*, 2016). In our study, *Stenotrophomonas maltophilia* was reported 2.7% which is comparatively low as compared to previous studies 4.2%, 17.9% and 7.3% conducted at Taiwan, Ethiopia and Turkey respectively (Chen *et al.*, 2010;

Aregaet *al.*, 2018; Yemisenet *al.*, 2016). We reported *Acinetobacter baumanni* 0.9%, which is almost same as study conducted in Pakistan while low as compared to study conducted by Siddiqui *et al.*, from Pakistan and Bajpal *et al.*, from India (Naz and Tariq, 2014; Wali *et al.*, 2012; Bajbal and Pandey, 2017). Present study reported 1.8% *Burkholderia cepacia,* while low as compared to Hannan *et al.*, from Pakistan and Bajpal *et al.*, from India (Hannan *et al.*, 2013; Bajpal and Pandey, 2017).

Table 6. Proportion of multidrug strains with various classes of antibiotics of non-fermenter gram negative bacteria causing blood stream infections in children.

Isolates	*Morganellamorganii*	*Stenotrophomonas maltophilia*	*Acinetobacter baumannii*	*Burkholderia cepacia*	Total MDR
MDR n(%)	00 (00)	02 (66.7)	01 (100)	02 (100)	05 (71.4)
Antibiotics Categories		1. Tetracyclines 2. Aminoglycosides 3. Penicillin/combination	1. Carbapenam 2. Cephalosporins 3. Aminoglycosides 4. Fluoroquinolones 5. Penicillin/combination	1. Carbapenam 2. Cephalosporins 3. Aminoglycosides 4. Penicillin/combination	

Antibiotic sensitivity pattern were different among same regions of the country but individually our reported *Morgenella morganii* resistance profile are consistent to the Azargun *et al.,* and Adams *et al.,* report for aztreonam, levoflxacin, imipenam, gentamicin, amikacin and cefipime (Azargun *et al.,* 2018; Adams *et al.,* 2012) while discordant with the report of Dimple *et al.*, 2016. Fewer studies regarding *Stenotrophomonas maltophila* were found in our setting, variation were observed among studies and present report about the antibiotics resistance profile of *Stenotrophomonas maltophila*. Imipenam and co-triamoxazole were highly sensitive to *Stenophomonas maltophila* which is almost in accordance to the report of Cho *et al.,* from Korea (Cho *et al.*, 2015). *Acinetobacter baumannii* were found emerging non-lactose fermenter bacterial isolate in present study due to high level of resistance to antibiotics. Only colistin/polymixin B were found more effective against *Acinetobacter baumannii* with 0% resistance which is similar to the results revealed by other studies (Ozdemir*et al.,* 2011).

Tazocin, imipenam, ciprofloxacin, ceftriaxone, gentamicin, ampicillin, amikacin and ceftazidime were found useless against Acinetobacter baumannii. Theses finding were almost consistent to the previous reports with little variation (Dimple *et al.*, 2016; Ozdemir *et al.,* 2011; Munoz e al., 2010; Gupta *et al.*, 2016). *Burkholderia cepacia* were more susceptible to tazocin and cefeperazone/sulbactam while varying with other reports (Adams *et al.,* 2012; Dimple *et al.*, 2016), whereas consistency were found with previous studies regarding gentamicin (Gupta *et al.*, 2016)), amikacin (Dimple *et al.*, 2016; Gupta *et al.*, 2016), ciprofloxacin, ceftriaxone (Naureen *et al.,* 2010) and cefipime (Tariq and Rasool., 2016).

The antibiotics resistance pattern vary from regions to regions in same area of the world which may be due to widely use of specific antibiotics in their hospital setting, transferred of resistant bacteria genes among bacterial isolate in overcrowded setup.

These four pathogens are leastly involved in clinical virulence but ESBL producing and multi drug resistance is often reported among these isolates. These microorganism are responsible for nosocomial outbreaks associated with contaminated antiseptics, intravenous fluids, saline solutions and disinfectants (Lugito*et al.,* 2016; Tang *et al.,* 2014; Siebor*et al.,* 2007; Bisharat*et al.,* 2007). These isolates are frequently reported from immunocompromised patients and children as an opportunistic and create emerging life threatening bacteremia (Lugito*et al.,* 2016; Tang *et al.,* 2014; Kwa *et al.,* 2008).

Table 7. Drug resistance pattern of recovered non-fermenter gram negative bacteria causing blood stream infections in children.

Antibiotics Classes Related to Number (%)						
Bacterial Isolates	Total n (%)	R_1	R_2	R_3	R_4	$>R_4$
Morganellamorganii	01 (14.3)	0	01	00	00	00
Stenotrophomonas maltophilia	03 (42.9)	00	01	02	00	00
Acinetobacter baumannii	01 (14.3)	00	00	00	00	01
Burkholderia cepacia	02 (28.5)	00	00	00	02	00
Total	07 (100)	00	02 (28.8%)	02 (28.6%)	02 (28.6%)	01 (14.2%)

R1: Bacteria resistant to single class/family of antibiotic
R2: Bacteria resistant to two class/family of antibiotic
R3: Bacteria resistant to three class/family of antibiotic
R4: Bacteria resistant to four class/family of antibiotic.

Antibiotics resistance is one of the worsen health care headache which is occur due to the inappropriate used or prescribing without having sensitivity report by clinicians.

They become aggravated with high morbidity and fatality rate. Secondly the resistance occurs because of incomplete course of such prescribed antibiotics due to high cost which is out of range of a middle class population especially in developing countries.

The resistance to antibiotics can be overcome with certain factors; prescribing according to the need and sensitivity report, stop freely availability of antibiotics in markets, regular appropriate surveillance to follow the risk agents and their pattern of antibiotics.

Conclusion

During this research project, we categorized the non-fermenter bacteria in multi-drug resistance together with extended spectrum beta lactamases production. We studied the proportion of non-fermenter gram negative isolates along with their resistance pattern which is significantly involved in blood stream infection particularly in children and immunocompromised patients. Future studies are required at molecular level to deepen the knowledge about our findings and clinical significance of these opportunistic bacteria.

Conflict of interest

Authors have no conflict of interest.

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