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Article

Prevalence of etiologic agents causing invasive bacterial disease and evaluation of their antibiotic susceptibility pattern

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Abstract: Invasive bacterial diseases (IBD) cause significant morbidity and mortality which leads to enormous health suffering and economic frustration in Bangladesh especially in people with resource poor region. The prevalence of IBD may vary even in different regions in a country. To understand the prevalence of etiologic agents causing IBD and determining their response to commonly used standard antibiotics we conducted a retrospective cross sectional study in rural town of Bangladesh on patient attended for blood culture with IBD sign-symptoms in well reputed microbiology lab. We considered IBD patients (118) of all age groups (0-85 years) both gender (male 54% and female 46%). 25% (30) blood culture of all IBD patients found bacterial growth positive including contaminant *Staphylococcus* sp. (10). The isolated IBD etiologic agents are *S. aureus* (10), *Salmonella* sp. (5), *Salmonella* Paratyphi (1), *E. coli* (2), *Shigella* sp. (1), *Pseudomonas* sp. (1). We could have retrieved antibiotic susceptibility testing data of five isolates including *S. aureus* (1), *Salmonella* sp. (2), *Salmonella* Paratyphi (1), *Pseudomonas* sp. (1); which showed except *Salmonella* sp. all isolates are sensitive to tested commonly used standard antibiotics. Two non typhoidal *Salmonella* sp. showed intermediate sensitivity to ciprofloxacin (5 µg) which indicate reconsideration of choosing non typhoidal *Salomonella* sp. infection with ciprofloxacin (5 µg). As it is a retrospective, not well organized cross sectional study; these findings may not represent the entire actual scenario of IBD in the region. As a consequence, a well organizing and adequately powered study must need to be conducted.

Keywords: invasive bacterial diseases; non typhoidal *Salmonella* sp.; antibiotic susceptibility

1. Introduction

Globally invasive bacterial diseases (IBD) are major cause of morbidity and mortality. In developing countries like Bangladesh IBD in children under 5 years is the significant public health problem. Invasive bacterial infection can be defined as the detection of bacteria in the normally sterile body fluids such as blood, cerebrospinal fluid (CSF), joint fluid, pleural fluid, pericardial fluid, bone aspirate, or a deep tissue abscess (Schuchat *et al.*, 2001). *Streptococcus pneumoniae, Haemophilus influenzae, Neisseria meningitidis, Streptococcus agalactiae, Streptococcus pyogenes, Staphylococcus aureus, Salmonella* species, *Listeria* species, and *Escherichia coli* are major bacteria involved in invasive infections in children especially in immunocompetent children (Nam and Lee, 1998; Lee *et al*., 2005). Most of the complications and mortality caused due to pneumonia, sepsis (Shann, 1995; Mullholland, 1999) and meningitis (Greenwood, 1987; Murray and Lopez, 1996). Pneumonia is the leading cause of mortality among the children under 5 years which globally

account to 19% per year (Jennifer *et al.*, 2005). *Streptococcus pneumoniae* and *Haemophilus influenzae* type-b are mainly involved in more than 50% and 20% of severe pneumonia cases with high mortality rate respectively (UNICEF/WHO, 2006).

Para-typhoid and typhoid fever are also the leading cause of child death (Denny and, Loda, 1886; Shann, 1986). Typhoid fever remains substantial public health concern in developing countries account to 16 million cases with 600,000 related deaths worldwide (Hossain *et al.*, 2000; Yichun, 2003).

Emerging of multiple drug resistance bacteria is a significant public health concern around the globe. In the case of invasive non-typhoidal *Salmonella* (iNTS) ciprofloxacin is recommended as first-line treatment and levofloxacin, moxifloxacin, cotrimoxazole, or the broad spectrum cephalosporins, ceftrioxone and cefotaxime are used as alternatives. Multidrug resistant NTS are involved in increased morbidity and are important health concern in both animals and humans. (Kariuki and Dougan, 2014; Guerrant *et al.*, 1990).

Because of lacking empirical data and evidence based intervention the use of the antibiotics has been increasing rapidly all over the world. Klein *et al*. (2018) have conducted a new global study which aimed to determine trends in antibiotics use from 2010-2015 in 76 countries. They compared total consumption of antibiotics between low-middle income countries (LMIC) e.g., India and China, and high-income countries (HIC) such as the UK and US. According to this study, between 2000-2015, global antibiotic consumption increased by 65% from 21.1 to 34.8 billion defined daily doses (DDDs), e.g. a single antibiotic capsule or injection – of antibiotics to 34.8 billion DDDs. The antibiotic consumption rate increased by 39% from 11.3 to 15.7 DDDs per 1,000 inhabitants per day over the 15 years of study periods. Increased consumption of antibiotics in the low- middle income countries was the primary reason for the increase in the global consumption. In low-middle countries antibiotic consumption raises 114% (11.4 to 24.5 billion DDDs) and the consumption rate increased 77% (7.6 to 13.5 DDDs per 1,000 inhabitants per day). Among LMICs India, China and Pakistan were the highest antibiotic consumers in 2015. In high-income countries (HICs) the total consumption of antibiotic increased by 6.6% (9.7 to 10.3 billion DDDs) and the rate of consumption increased by 4% (26.8 to 25.7 DDDs per 1,000 inhabitants per day). In 2015 US, France and Italy were the highest antibiotic consumer among HICs (Klein *et al*., 2018). Over use or injudicious use of antibiotics may contribute in emerging of multi-drug resistant bacterial strain.

In this retrospective cross sectional study, we aimed to assess the prevalence of invasive bacterial disease causing etiologic agents and their antibiotic susceptibility pattern in a rural town in Bangladesh from January to September 2018.

2. Materials and Methods

2.1. Patient criteria

We retrospectively collected the data of 118 patients who meets WHO criteria of invasive bacterial disease (IBD) and performed blood culture in a reputed microbiology laboratory in Bangladesh.

2.2. Blood collection and processing

BD Bactec-120 system has been used for blood culture along with combination of conventional plate culture method. 1-3 ml of blood were taken in Bactec PD Plus Aerobic Blood Culture bottle and inserted into Bactec-120 machine, and incubated at 35.5°C for 5 days. Bactec fluorescent series instrument has made significant impact on laboratory blood culture practice by enhancing sensitivity and reducing time to detect numerous pathogens in blood. This instrument swiftly detects presence of microorganisms in Bactec Ped Plus/F culture vials (containing Soyabean Casein Digest Broth and other necessary ingredients) and produces a positive signal based on detecting CO_2 in growth media. After getting positive signal from the machine, it was suspected that there might presence some organisms or pathogens, then the positive culture bottle was taken out from the machine and sub-cultured on to three media plates such as Blood agar, Chocolate agar and MacConkey agar. The organisms are then finally identified on the basis of their morphological characteristics including size and shape of the organism, arrangement of the cells, presence or absence of the spores, regular or irregular forms, acid fastness, gram reaction etc.; cultural and physiological characteristics including H_2S production, nitrate reduction, deep glucose agar test, fermentation of different carbohydrates etc. All these characteristics were then compared with the standard description of ‘‘Bergey’s Manual of Determinative Bacteriology’’, 8th edition (Buchanan and Gibbons, 1974).

2.3. Antibiotic susceptibility testing

Antibiotics susceptibility test was performed by Kirby-Bauer disc diffusion method (Hudzicki, 2009). Bacterial suspensions were prepared from fresh culture grown overnight onto nutrient agar plates by using sterile normal saline and the turbidity of the suspension was adjusted to 0.5 McFarland Standard that corresponds to

approximately $1x10^8$ CFU/mL of suspension. A sterile cotton swab was dipped into the inoculum then streaked on the Mueller-Hinton agar plate properly. Then antibiotic discs impregnated with selected antibiotic discs for each isolate were dispensed onto the dried agar surface using a sterile forceps. The plates were incubated overnight at 37°C. After incubation period, the resulted zone of inhibition was compared with that of Clinical and Laboratory Standard Institute guideline (CLSI, 2018) for the interpretation of the data and categorization of the test strains as intermediate, sensitive, or resistant (Uddin *et al.*, 2017)

3. Results and Discussion

We have retrospectively collected data of 118 patients with invasive bacterial diseases (IBD) of different age groups (0-85 years) (Figure 1) whose 54% (64) are male and 46% (64) are female (Figure 2). Among them 26.5% (31) are 5 or below 5 years of age, 14.53% (17) are 6-10 years of age. More than half (58%) of the patient enrolled in this study are of less than 21 years of age.

We found that 25% (30) blood cultures of enrolled patient (118) in the study is positive growth with any organisms. *S. aureus* (38%) and *Staphylococcus* sp. (38%) are found as more dominant organisms. *S. aureus* are involved in diverse range of clinical complications including asymptomatic colonization, skin and soft tissue infection and bone and joint infections. *S. aureus* is major pathogen of community-acquired pneumonia in children <5 years of age (Schwartz and Nourse, 2012). *Staphylococcus* sp. is considered as contamination from the skin which indicates aseptic techniques were not maintained properly during collecting blood. *S. aureus* is an opportunistic pathogen in blood as it is normal flora in the skin. *S. aureus* showed sensitivity to amphicillin (25 µg), netilmicin (30 µg), ciprofloxacin (5 µg), amikacin (30 µg), gentamicin (10 µg), cloramphenicol (30 µg), cotrimoxazole (25 µg), ceftriaxone (30 µg), azithromicin (15 µg), ceftazidime (30 µg), clindamicin (2 µg) and penicillin (10 unit) (Table 1). As we found *S. aureus* was sensitive to all antibiotics used in this study including gentamicin and ciprofloxacin which are in agreement with other reports from Bangladesh (Ashrafudoulla *et al*., 2017) and other part of the world (Olayinka *et al.*, 2010). In the USA in 2005, an estimated 94 000 invasive MRSA infections required hospitalization and were associated with 19 000 deaths (Klevens *et al.*, 2007). However, emergence of multidrug resistant *S. aureus* has been reported from different parts of the world (Kumar, 2016; Adebola and Tarilate, 2011) as well as from Bangladesh (Ashrafudoulla *et al*., 2017).

In this study, 17% (3) of all etiologic agents causing invasive bacterial diseases (IBD) is *Salmonella* sp. The other etiologic agents of invasive bacterial diseases (IBD) are *E. coli* (7%), *S*. Paratyphii (3%), *Shigella* sp. (3%) and *Pseudomonas* sp. (3%) etc. (Figure 3). We found that *S*. Paratyphii and *Salmonella* sp. are sensitive to amphicillin (25 µg), netilmicin (30 µg), amikacin (30 µg), gentamicin (10 µg), cloramphenicol (30 µg), cotrimoxazole (25 µg), ceftriaxone (30 µg), azithromicin (15 µg) and cefixime (5 µg) and intermediate sensitive to ciprofloxacin (5 µg) which denotes that ciprofloxacin (5 µg) is losing its preference to treat patient with invasive disease infected with *S*. Paratyphi and *Salmonella* sp. (Table 1).

Table 1. Antibiotic susceptibility testing (AST) results of some etiologic agents (Diameter of zone of inhibition in mm).

Specimen ID	Organisms	Amphicillin	Netilmicin	Ciprofloxacin	Amikacin	Gentamicin	Chloramphinicol	Cotrimoxazole	Ceftriaxone	Azithromicin	Ceftazidime	Clindamicin	Cefixime	Penicillin	Piperacillin
M311	*S.* Paratyphii	22(S)	34(S)	26(I)	28(S)	28(S)	22(S)	28(S)	28(S)	16(I)	-	-	26(S)	-	-
M328	*Salmonella* sp.	28(S)	26(S)	28(I)	24(S)	25(S)	26(S)	32(S)	28(S)	20(S)	-	-	30(S)	-	-
M361	*Salmonella* sp.	20(S)	32(S)	22(I)	28(S)	32(S)	20(S)	26(S)	28(S)	18(S)	-	-	26(S)	-	-
M330	*S. aureus*	32(S)	20(S)	28(S)	26(S)	28(S)	26(S)	30(S)	30(S)	26(S)	22(S)	26(S)	-	34(S)	-
M336	*Pseudomonas* sp.	26(S)	26(S)	24(S)	24(S)	26(S)	22(S)	30(S)	31(S)	24(S)	28(S)	-	26(S)	-	24(S)

*S-Sensitive; I-Intermediate;

**Results interpreted according CLSI guide line 2018.

Previously in invasive non-typhoidal *Salmonella* (iNTS) endemic sub sarahan African countries, co-trimoxazole, ampicillin or chloramphenicol were used as first-line treatment for enteric and iNTS diseases.

However, due to raising prevalence of iNTS which are resistant to commonly used antibiotics, broad spectrum cephalosporins and fluoroquinolones replaced these older agents from the late 1880s. Fluoroquinolone resistance among NTS is an increasing problem. In 1990 ciprofloxacin resistant *Salmonella enteric* was reported for the first time (Nath *et al.*, 2000). Since then, there have been several reports of ciprofloxacin resistant isolates from different countries including India, Pakistan, Vietnam, Spain and Malawi. (Piddock *et al.*, 1990; Menezes *et al.*, 2010). Multidrug resistant *Salmonella* Typhi and *Salmonella* Paratyphi A is a great problem in endemic areas and returning travellers (Wain *et al.*, 2015). In the late 1980s and 1990s, chloramphenicol, ampicillin and co-trimoxazole resistant isolates of Typhi and Paratyphi were involved in large outbreaks in Asia (Arjyal *et al.*, 2011). Ciprofloxacin and Ofloxacin have been broadly recommended for treatment in the last two decades for the patients including children (Effa *et al.*, 2001. Crump *et al*. (2008) reported the emergences of intermediate level ciprofloxacin resistant isolates which supports our study. This is may be due to extensive use of ciprofloxacin. High-level fluoroquinolone resistance isolates are now commonly found in the Indian sub-continent but are also emerging in Africa (Gaind *et al*., 2006; Feasey *et al*., 2014; Koirala *et al.*, 2013).

Pseudomonas sp. showed sensitivity to amphicillin (25 µg), netilmicin (30 µg), ciprofloxacin (5 µg), amikacin (30 µg), gentamicin (10 µg), cloramphenicol (30 µg), cotrimoxazole (25 µg), ceftriaxone (30 µg), azithromicin (15 µg), ceftazidime (30 µg), cefixime (5 µg) and piperacillin (100 µg) (Table 1). Emergence of multidrug resistant *Pseudomonas* has attracted the attention of many researchers in recent decades (Gomez *et al.*, 2012). According to a recent report by The European Antimicrobial Resistance Surveillance Network (EARS-Net), among *P. aeruginosa* invasive isolates, the mean resistance percentages for piperacillin/tazobactam, carbapenems and fluoroquinolones were close to 20%, while for ceftazidime and aminoglycosides they were 13% (EARS-Net, 2015). In Europe between 2011 and 2015, carbapenem and ceftazidime resistance trend of *P. aeruginosa* didn't change but raise of piperacillin resistant isolates was observed (EARS-Net, 2015). There were higher resistance rates in the southern and Eastern Europe compared with the northern countries (EARS-Net, 2015). According to a report from Spain, higher resistance rates for piperacillin/tazobactam, ceftazidime, fluoroquinolones and aminoglycosides (with the exception of amikacin) than those reported by EARS-Net (EARS-Net, 2015; Cabot *et al.*, 2011). High Ampicillin resistant isolates were reported from Bangladesh (Nasreen *et al*., 2015), Pakistan (Anjum and Mir, 2010) and India (Krishnakumar *et al.*, 2012). Isolates which showed high resistance to Gentamicin were also found in Bangladesh (Rashid *et al.*, 2007), Egypt, India (Raja and Singh, 2007), Iran (Saderi *et al.*, 2010), and Pakistan (Naqvi *et al.*, 2005). Previously Co-trimoxazole resistant isolates were found in Bangladesh (Rashid *et al.*, 2007; Nasreen *et al*., 2015). Rashid *et al*. (2007) found ciprofloxacin resistant *P. aeruginosa* in Bangladesh. But another study conducted by Nasreen *et al*. (2015) found no ciprofloxacin resistant isolates, which observation is similar to ours.

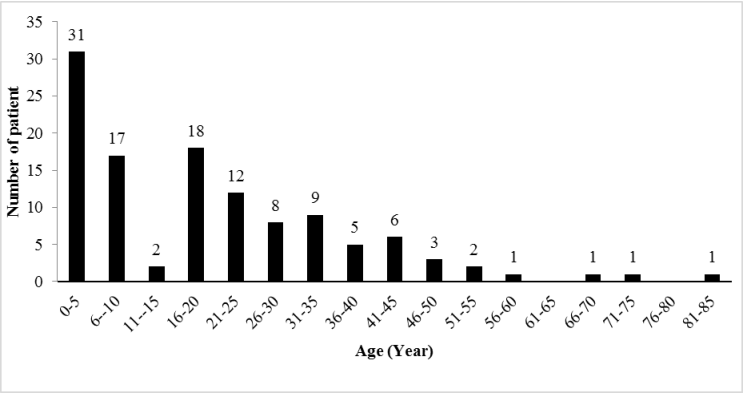

Figure 1. Age distribution of the patients with invasive bacterial diseases (IBD) (Total patient: 117 as we missed age of one patient).

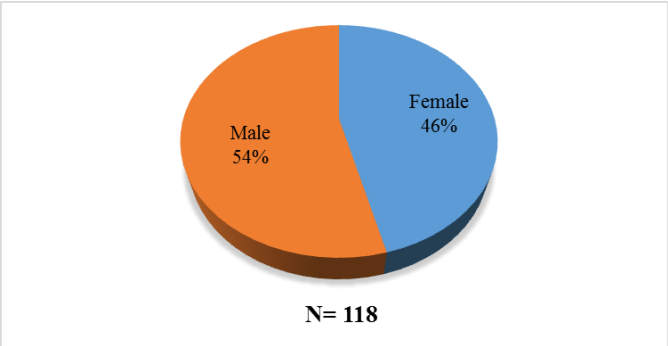

Figure 2. Patients with invasive bacterial diseases (IBD) enrolled in the study were 54% male and 46% female.

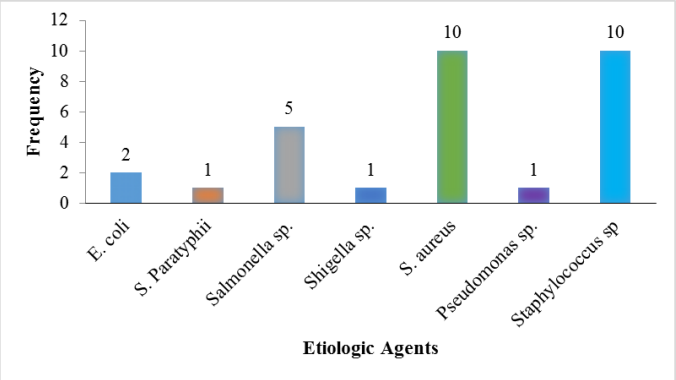

Figure 3. Distribution of etiologic agents causing invasive bacterial diseases (IBD).

4. Conclusions

Though this study was not well designed and not adequately powered but it brought some lights in to prevalence of invasive bacterial disease causing by non typhoidal *Salmonella* (NTS) and *S. aureus* and their response to commonly used antibiotics. We advised further study needed to be conducted to delineate the entire scenario of invasive bacterial diseases.

Conflict of interest

None to declare.

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