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Short Communication

Drug Resistance Associated with Blood Borne Bacteria in Dhaka Metropolis

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Blood borne infections are easy to contract during hospital procedures and can easily be transferred to other personnel in a healthcare setting. Bacteremia has become a common incidence and treatment is by administration of antibiotics. But this is not a simple task any more, since the pathogenic bacteria causing bacteremia are becoming resistant to a wide range of antibiotics. Blood samples were collected from outdoor patients seeking laboratory tests in Dhaka city. Blood samples were inoculated onto blood agar medium and after incubation for 37ºC for 24 hours, bacterial isolates were identified and subjected to antibiotic susceptibility test by following the Kirby-Bauer method. The current present study deals with 100 patients of bacteremia from whom 150 isolates of 15 different bacterial genera have been collected among which the most prominent bacteria were *Staphylococcus* spp. (51 isolates), *Pseudomonas* spp. (19 isolates) and *Escherichia* spp. (19 isolates). After the antibiotic susceptibility test it was found that all isolates were resistant to a number of commonly used antibiotics. Twenty eight different antibiotics were used for this study. All isolates showed resistance to CAR, ATM, TOB, CXM, FD, CL, CAZ, AMC. NET and CN showed the most effective results (can effectively clear 9 and 10 types of isolates respectively found in this study). New discovery of drugs to fight these resistant pathogens is needed. In the meantime, safe administration of drugs, handling patients with appropriate protective personal clothing and apparatus, proper waste disposal managements in the hospital should be maintained strictly.

Key words: Antibiotic, pathogen, drug resistance, bacteremia.

Introduction

Systemic infections with the involvement of blood contaminated with pathogenic microorganisms is a serious issue which often leads to difficulty in treatment as well as high mortality rate[1, 2]. Microorganisms can gain entrance through different ways. A good number of microorganisms from both gram positive and gram negative groups has been confirmed to cause bacteremia- bacterial infection in blood. *Staphylococcus aureus, Streptococcus pneumoniae*, *Streptococcus anginosus, Salmonella* spp., *Pseudomonas aeruginosa*, *Acinetobacter* spp, *Enterobacter* spp., *Corynebacterium* spp, *Bacillus* spp, *Clostridium* spp., *Haemophilus influenzae, Neisseria meningitidis, Rhodococcus equi., Streptococcus bovis*, *Escherichia coli*, *Aeromonas* spp., *Serratia marcescens, Listeria monocytogenes*[3-6]. Treatment of bacteremia is quite difficult specially in case of gram positive bacteria [5]. Among them MRSA- methicillin resistant *Staphylococcus aureus* is the most common causing bacteremia in European countries capable of causing infective endocarditis and metastatic infections[7-10]. The factors responsible for transportation of the bacteria includes central venous catheter, urinary catheter, cellulitis, ulcer, injecting drugs, surgical wounds, immunosuppression etc[11-13]. The other most prominent community acquired as well as common nosocomial bacteremia in United States is *Escherichia coli*[14-19,5]. Though *E. coli* is a commensal in human body, under some circumstances it causes opportunistic infection. Predisposing factors include people over 65 years old, specially women. The portal of entry was mostly urinary tract and gastrointestinal tract[20].

Bacteremia occurs mainly in patients with immune deficiencies. One major cause of such immunodeficiency is HIV infection. Some factors influence the bacteremic condition such as central venous catheters, high rate of intravenous drug administration, defects in cell mediated immunity (CD-4), neutropenia etc. Some portals of entry includes genitourinary tract, respiratory tract, gastrointestinal tract, broken skin etc. A common problem is due to non-typhoidal *Salmonella* spp[21-22]. Though the morbidity and mortality rate is high two steps can be taken at a time to lessen the situation. One involves antiretroviral drug administration for controlling HIV and adequate prolonged antibiotic treatment for the bacteremia[23-26].

Piercing and tattoo involves with the injections which come in contact with blood. In case of tattoo colors are injected under the skin and there is a great chance of contamination during the whole process[27-30]. The needle used for tattoo once used for a person infected with HBV, HCV, HIV etc can transmit to other person while injecting[31-37].

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Health care workers are at a high risk of exposure to blood borne pathogenic microorganisms from the infected patient during some medical procedures involving sharp needles, scissors, or any broken sharps contaminated with blood of the patient. After that, the health care workers further disseminate the infection to other patients through the same process. About 25% cases bacteremia are hospital acquired[38].

Pathogenesis of bacteremia occurs step by step. For example, Staphylococcal isolates at first adhere and colonize through broken skin and mucus membrane following connection with blood. Adherence factor is also a virulence factor for this bacteria. They produce different enzymes and toxins to hydrolyze tissue and disseminate towards other parts through blood. Such protein material are recognizable as virulence factors[39-43].

To diagnose the bacteremic condition some tests should be done to detect the pathogen. The diagnostic tests include transthoracic-transesophageal echocardiography, radiography, positronemission tomography, CT, WBC count, C-reactive protein level measurement etc to detect deep seated infections. The samples are blood samples collected from venous catheters. Blood cultures to identify pathogens followed by PCR and fluorescent based methods are popular for diagnostic purposes. The infection responsible to cause bacteremia should be identified. Sometimes local pus, abscess, scars etc physical findings occurs after the systemic condition which makes the phenomena even worst[1,44-46].

The treatment starts right after the detection of positive test results. But if contamination occurs in the blood culture and shows a false positive result which actually is of no relation with the patient [47-49]. In the same way, false negative test result is not desirable. Patients with blood infections may not show positive result increasing the mortality and morbidity rate because of proper treatments. This happens specially for pneumococcal infections. Presence of *Pneumococci* can be showed in blood culture within 12 hours but not after 24 hours. In case of counter immune electrophoretic method, the same phenomena happens; negative result after 24 hours. *Streptococcus pneumoniae* often shows such false negative result[50].

In the current study about 100 patients were selected to determine bacterial isolates from both male and female patients of different ages and to determine drug sensitivity patterns of the isolates.

Materials and method

Study area and sampling

About 100 male and female patients were randomly selected who were of different ages. Patients were selected from Dhaka city seeking for treatments. The experiment was conducted within February, 2016 and May, 2016. Blood samples were collected aseptically and immediately transferred to different culture media. Personal protective equipment and clothing was strictly maintained to avoid any hazards and transmissions so healthcare workers and to others.

Identification of bacterial isolates

Bacterial isolates found in the blood agar plates were detected following the biochemical identification. Different biochemical tests like TSI, MIU, catalase, oxidase, citrate utilization test, MR, VP were conducted to confirm the identification of the isolated bacteria.

Detection of antibacterial susceptibility pattern

Blood samples were subjected to inoculate aseptically on nutrient agar and blood agar plates to find the bacterial colonies present in the blood sample. After 48 hours of incubation all the bacterial colonies were subjected to biochemical identification to get the identification of the blood borne bacteria. The main part of the case study was the susceptibility pattern of the isolates against the popular antimicrobials used in Bangladesh. For this work, bacterial suspensions of the isolated bacteria (*Staphylococcus* spp., *Pseudomonas* spp., *Escherichia* spp., *Klebsiella* spp., *Proteus vulgaris*, *Acinetobacter* spp., *Citrobacter* spp., *Enterobacter* spp., *Enterococcus* spp., *Streptococcus* spp., beta hemolytic *Streptococcus* spp., *Moraxella* spp. and *Providentia* spp.) were prepared in normal saline separately and incubated at 37^{o}C. After matching the suspensions with 0.5 McFarland standard, they were inoculated onto the Mueller Hinton agar plates to make a lawn of bacterial suspension. After that 28 different antibiotic discs (Netilmicin, Trimethoprim-Sulphamethoxazole, Fusidic acid, Ciprofloxacin, Oxacillin, Vancomycin, Tobramycin, Carbenicillin, Imipenem, Cefalonium, Amoxicillin, Azithromycin, Ceftriaxone, Tigecycline, Cefotaxime, Cefoxitin, Cefuroxime, Piperacillin-Tazobactam, Ceftazidime, Cefepime, Fusidic acid, Clindamycin, Chloremphenicol, Amikacin, Colistin, Gentamicin, Rifampin, Radicicol) were aseptically placed over the bacterial lawn. After 24 hours incubation at 37^{o}C plates were observed for the presence of the zone of inhibition and measured in millimeter scale to determine whether the pathogenic isolates were antibiotic resistant or sensitive.

Results

Isolated bacteria were subjected to biochemical test for proper identification after doing the tests we found *Escherichia* spp., *Staphylococcus* spp., *Streptococcus* spp., *Pseudomonas* spp., *Klebsiella* spp., *Proteus* spp., *Providentia* spp., *Moraxella* spp., *Enterobacter* spp., *Citrobacter* spp., *Acinetobacter* spp. and *Enterococcus* spp.

In the current study, 129 isolates of 12 types of bacteria collected from blood were subjected to antimicrobial susceptibility test to determine the drug resistance patterns. Most predominant isolate was *Staphylococcus* spp. (51 patients). *Pseudomonas* spp. (19 patients), *Escherichia* spp. (19 patients), *Proteus* spp. (12 patients) were also found in the bacteremic patients. The less frequent bacterial isolates found from the patients were *Klebsiella* spp., *Acinetobacter* spp., *Citrobacter* spp., *Enterobacter* spp., *Enterococcus* spp., *Streptococcus spp.*, *Moraxella* spp. and *Providentia* spp.

Table 1. *Biochemical identification of the isolated bacteria.*

	Slant	Butt	Gas	H_2Sreaction	Indole test	MR test	VP test	Citrate test	Motility	Oxidase test
Klebsiella spp.Y	Y	-	-	-	-	-	-	-	+	
Enterococcus spp.	Y	Y	-	-	-	-	+	-	-	-
Staphylococcus spp.	Y	R	+	+	-	+	-	+	+	-
Streptococcus spp.	Y	Y	-	-	-	+	-	-	-	-
Citrobacter spp.	Y	Y	+	+	-	+	-	+	+	-
Acinetobacter spp.	R	R	-	-	-	-	-	+	-	-
Enterobacter spp.	Y	Y	+	-	-	-	+	+	-	-
Moraxella spp.R	R	-	-	-	+	-	-		+	
Providentia spp.	R	R		-	+	+	-	+	+	-
Pseudomonas spp.	Y	Y	-	-	-	-	-	+	-	-
Escherichia spp.	Y	Y	+	-	+	+	-			
Proteus spp. Y	Y	+	+	-	-	+	+	+	+	

Table 2. *Drug resistance trait of the isolates collected from blood sample.*

Antibiotics	Klebsiella spp. (n=9)	Escherichia spp.(n=19)	Pseudomonas spp. (n=19)	Proteus spp. (n=12)	Staphylococcus spp. (n= 51)	Acinetobacter spp. (n=2)	Citrobacter spp. (n= 1)	Enterobacter spp. (n=4)	Enterococcus spp. (n=6)	Streptococcus spp. (n=2)	Moraxella spp. (n=3)	Providentia spp. (n=1)
NET	R(100%)	S(90%)	S (70%)	S(70%)	S(90%)	S(100%)	R(100%)	R (75%)	S(100%)	S(100%)	S(100%)	R(100%)
CN	R(100%)	S(90%)	S (80%)	S(80%)	S(80%)	R(100%)	R(100%)	R(100%)	S(80%)	S(100%)	S(100%)	R(100%)
AK	R (70%)	S(70%)	S (90%)	S(100%)	S(70%)	R(100%)	R(100%)	R(75%)	R(100%)	R(50%)	S(100%)	R(100%)
IMP	R(70%)	S(80%)	S(90%)	S(100%)	-	R(100%)	R(100%)	S(100%)	-	-	S(100%)	S(100%)
TZP	R(100%)	S(100%)	R(100%)	S(100%)	-	R(100%)	R(100%)	S(100%)	-	-		S(100%)
CFM	R(70%)	R(100%)	R(100%)	R(80%)	-	R(100%)	R(100%)	S(75%)	-	-	R(100%)	R(100%)
AMC	R(90%)	R(90%)	R(90%)	R(70%)	R(60%)	R (100%)	R (100%)	R (75%)	-	-	R(100%)	R(100%)
CRO	R(100%)	R(100%)	R(80%)	R(70%)	-	R(100%)	R(100%)	S(100%)	-	-	R(100%)	R(100%)
CAZ	R(100%)	R(80%)	R(90%)	R(60%)	-	R(100%)	R(100%)	R(100%)	-	-	R(100%)	R(100%)
CTx	R(90%)	R(100%)	R(100%)	R(50%)	-	R(100%)	R(100%)	S(100%)	-	-	R(100%)	R(100%)
FEP	R(60%)	R(70%)	R(70%)	R(50%)	-	R(100%)	R(100%)	S(100%)	-	-	R(100%)	R(100%)
CT	S(100%)	S(100%)	S(100%)	R(100%)	R(70%)	S(100%)	S(100%)	S(100%)	-	-	R(100%)	R(100%)
SXT	R(100%)	R(80%)	S(80%)	R(100%)	S(80%)	R(100%)	R(100%)	R(100%)	R(80%)	R(100%)	S(100%)	R(100%)
CIP	R(90%)	R(90%)	S(80%)	R(70%)	S(70%)	R(100%)	R(100%)	R(100%)	S(100%)	S(100%)	S(100%)	R(100%)
OX	-	-	S(100%)	-	R(80%)	-	-	-	-	-	-	-
FOX	-	-	S(90%)	-	R(80%)	-	-	-	-	-	-	-
CL	-	-	R(100%)	R(100%)	R(70%)	-	-	-	-	-	-	-
CXM	-	-	R(100%)	-	R(80%)	-		-	-	-	-	-
FUS	-	-	R(100%)	-	S(60%)	-	-	-	-	-	-	-
RD	-	-		-	S(80%)	-	-	-	-	-	-	-
VA	-	-	S(100%)	-	S(90%)	-	-	-	S(100%)	S(100%)	-	-
DA	-	-	R(100%)	-	S(70%)	-	-	-	-	-	-	-
RA	-	-	R(100%)	-	S(90%)	-	-	-	-	-	-	-
TOB	-	-	-	-	-	-	-	R(100%)	-	-	-	R(100%)
ATM	-	-	-	-	-	-	-	R(75%)	-	-	-	R(100%)
TGC	-	-	-	-	-	-	-	S(100%)	-	-	-	S(100%)
CAR	-	-	-	-	-	-	-	R(100%)	-	-	-	R(100%)
FD	-	-	-	-	R(100%)	-	-	-	-	-	-	-

NET= Netilmicin, SxT= Trimethoprim-Sulphamethoxazole, FUS= Fusidic acid, CIP= Ciprofloxacin, Ox= Oxacillin, VA= Vancomycin, TOB= Tobramycin, CAR= Carbenicillin, IMP= Imipenem, CFM= Cefalonium, AMC= Amoxicillin, ATM= Azithromycin, CRO= Ceftriaxone, TGC= Tigecycline, CTx= Cefotaxime, FOX= Cefoxitin, CXM= Cefuroxime, TZP= Piperacillin-Tazobactam, CAZ= Ceftazidime, FEP= Cefepime, FD= Fusidic acid, DA= Clindamycin, CL= Chloremphenicol, AK=Amikacin, CT= Colistin, CN= Gentamicin, RA= Rifampin, RD= Radicicol

From the result table, it is clear to understand that all of the isolates have already become resistant to many antibiotics which are used very commonly in our country. Many drugs have become 100% resistant according to the isolates. For example, the isolates showed 100% resistance towards CAR, ATM, TOB, CXM, FD, CL, CAZ, AMC. NET, CN, IMP have been shown to be the most effective drugs to which maximum isolates were susceptible. All the isolates were susceptible to VA (*Pseudomonas* spp., *S. aureus*, *S. epidermidis*, *Enterococcus* spp., *S. pyogenes*, *S. agalactiae*) which were subjected to it, *Enterococcus* spp., *Providentia* spp., *Staphylococcus* spp. towards RD. 75% to 90% resistance was shown to other antibiotics.

Discussion

To treat the bacterial infection antibiotic administration is the most effective way. But the effectiveness has been compromised with the drug resistance traits of the pathogenic isolates which render the infections difficult to treat. As a result mortality rate due to the infections are rising. In the present study, 100 patients (both male and female) having blood borne infections were selected to determine the causative agent of the bacteremia as well as the degree of antibiotic drug resistance traits. Shockingly it was observed that the bacterial isolates found from the blood samples are highly resistant towards the antibiotics which are popularly used by the physicians to treat bacteremic patients. For example, the most predominant pathogen *Staphylococcus aureus* was already resistant to seven popularly used antibiotics (AMC, CT, OX, FOX, CL, CXM, FD). In contrast, *Providentia* spp. was susceptible only to two antibiotics (IMP, TZP). One of the most common pathogenic agents *Klebsiella* spp. was found to be susceptible only to the antibiotic CT. This kind of finding represents an alarming condition of Bangladesh where treating bacteremic patients is getting difficult and if not controlled the treatment procedure will become much more challenging.

From Table 04 it is clear that the bacteria found in blood, showed resistance towards different antibiotics From this table we can state that the drug resistance pattern is growing very fast and the time is not so far when all the remaining susceptible antibiotics will also become ineffective.

The resistance mechanisms are different for different organisms. For example, *Pseudomonas aeruginosa* can survive by multidrug efflux mechanism controlled by the transcription regulator encouraging the drug resistant gene expression [53-56]. *Salmonella enterica* has been found to be resistant against â lactam antibiotics by producing â lactamases[57-59]. Many pathogenic isolates can produce aminoglycoside modifying enzymes which add the features of aminoglycoside resistance[32]. Aminoglycoside 6-*N*-acetyltransferase type Ib is now a clinically important enzyme which has been found in many Gram positive bacteria which confer them resistance to aminoglycosides[60]. Mutations in ribosomal protein S 5in *Neisseria gonorrhoeae* decrease susceptibility to spectinomycin, cefixime and ceftriaxone[61]. Methicillin resistant *Staphylococcus aureus* is also very common in the world[62].

Drug resistance genes can be transferred to other susceptible microorganisms with the help of plasmids and virus. Genetic recombination, insertion of new resistant genes are very common in the case of transferring new drug resistant genes. Mutations in

Table 3. *Distribution of pathogenic bacteria causing bacteremia in Dhaka city from 2005 to 2016[51].*

Etiological agents	Bacteremia during the time period of 2005 to 2014	Bacteremia in 2016	Changes
Most predominating pathogenic bacteria	Salmonella Typhi	Staphylococcus aureus	Blood borne infection by Salmonella spp. drastically decreased and previously common etiologic agent *Staphylococcus* spp. *(S. aureus)* has become the most predominant pathogenic bacteria.
Other frequently isolated bacteria	*Staphylococcus spp., Pseudomonas spp., Acinetobacter spp., Salmonella paratyphi A,B, Klebsiella spp, E. coli, Enterobacter spp., Serratia spp, Klebsiella spp.*	*Pseudomonas, E. coli, Proteus vulgaris, Klebsiella* spp.	Some commonly found bacteria are steadily causing bacteremia (Pseudomonas, E. coli, Klebsiella spp.). New agent has been emerged such as Proteus vulgaris.
Occasionally found pathogenic bacteria	*Streptococcus* spp.	*Enterococcus spp., Enterobacter spp., Streptococcus spp., Acinetobacter spp., Citrobacter spp., Providentia* spp.	New groups of bacteria emerged (*Citrobacter* spp., Providentia spp.). Previous frequently encountered bacteria (*Enterobacter* spp., *Acinetobacter* spp.) decreased and become occasional pathogenic agents.

Table 4. *Changes in the drug resistance pattern from the past to the recent year-2016 in perspective of Bangladesh* [51, 52].

Pathogenic bacteria	Increasing trend of resistance to antibiotics before 2016	Resistance to antibiotics in the year of 2016
Escherichia coli	Ampicillin, Gentamicin, Ciprofloxacin, Ceftriaxone, Netilmicin, Amikacin, Imipenem, Ceftazidime, Cefixime.	Trimethoprim-Sulphamethoxazole, Ciprofloxacin, Cefalonium, Amoxicillin, Ceftriaxone, Cefotaxime, Ceftazidime, Cefepime.
Staphylococcus aureus	Trimethoprim-Sulphamethoxazole, Ciprofloxacin, Ceftriaxone, Chloremphenicol, Gentamicin, Erythromycin	Oxacillin, Amoxicillin, Cefoxitin, Cefuroxime, Fusidic acid, Chloremphenicol, Colistin.
Streptococcus spp.	Erythromycin, Azithromycin	Trimethoprim-Sulphamethoxazole, Netilmicin, Amikacin
Enterococcus spp.	Fusidic acid, Amikacin, Gentamicin, Netilmicin, Ciprofloxacin, Chloramphenicol, cotrimoxazole.	Amikcin, Trimethoprim-Sulphamethoxazole.
Pseudomonas spp.	Aztreonam,, cefotaxime, ceftriaxone, chloramphenicol, , colistin, gentamicin, imipenem, netilmicin	Fusidic acid, Cefalonium, Amoxicillin, Ceftriaxone, Cefotaxime, Cefuroxime, Piperacillin-Tazobactam, Ceftazidime, Cefepime, Clindamycin, Chloremphenicol, Rifampin.
Acinetobacter spp.	Cefotaxime, Ceftriaxone, Ciprofloxacin, Gentamicin, Netilmicin, Piperacillin and Tazobactam combination, Amikacin, Ceftazidime	Trimethoprim-Sulphamethoxazole Ciprofloxacin, Imipenem, Cefalonium, Amoxicillin, Ceftriaxone, Cefotaxime, Piperacillin-Tazobactam, Ceftazidime, Cefepime, Amikacin, Gentamicin,

the genetic material is also another mechanism. Such conditions have worsened the course of treatment due to lack of effective antibiotics. New drugs are needed to be produced for such conditions.

Resistant bacteria can transmit to other healthcare workers accidentally by sharps and they (healthcare workers) can transfer these bacteria to other patients if proper protective clothing and apparatus are not used. In medicals the unsterilized patient samples and garbage containing the contaminants may also allow the drug resistant pathogens to spread in the environment. So medical disposals should be under strict supervision of law and the medical authority. People infected with the drug resistant bacteria can be treated with only a few antibiotics This condition is driving the scientists to discover new antibiotics to treat drug resistant isolates.

Conclusion

The present study reflects a very alarming scenario in the medical science where almost all kinds of pathogenic bacteria responsible for causing bacteremia have become resistant to a wide range of antibiotics. Only a few antibiotics are till now effective. But there is a chance of these antibiotics to become resistant in the future. So necessary steps should be followed by the healthcare professionals and patients together in taking the medications and awareness about the transmissions.

The complications of drug resistance has become a major threat in Bangladesh and it is necessary to get the attention of the scientific community to understand the upcoming devastating condition in the medical era. About 100 bacteremic patients who were subjected to drug resistance test before treatment, alarmingly showed that all pathogenic bacteria responsible for causing bacteria were resistant towards maximum types of antibiotics which are generally prescribed in our country. A large number of patients are in a life threatening condition because the infection is not recovering by the conventional antibiotic therapy. Moreover, the resistance genes can render other susceptible bacteria into resistant ones through plasmids and other mobile elements. So, it is needed to check this problem by proper dosage, patient awareness and investigation for newer therapeutics.

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