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Original Research Article

Bloodstream Infections and Antimicrobial Susceptibility Patterns. A study in a tertiary care hospital in Bangladesh

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Abstract

Bloodstream infections due to bacterial pathogens are a major cause of morbidity and mortality in Bangladesh and other developing countries. In these countries, most patients are treated empirically based on their clinical symptoms. In the perspective of Bangladesh, people are taking medication without consulting a physician and this is the true reason for the emergence of drug resistance. Blood stream infection (BSI) due to bacterial pathogens is a global concern. The aim of this study was to identify the bacterial pathogens causing major bloodstream infections in Brahmanbaria, Bangladesh and determine their antibiotic susceptibility pattern. Two hundred and fifteen blood samples from 215 patients suspected of having BSI were cultured as per standard microbiological procedures. Antimicrobial susceptibility testing was done for bacterial isolates from positive blood cultures. 17 % cases were established as BSI. *Staphylococcus aureus* were most prevalent (51 %), followed by *Enterococcus faecalis* (16 %) *Escherichia coli* (11%), *Klebsiella pneumoniae (8 %),* Enterobacter spp (5%), *Pseudomonas aeruginosa* (6%), *Proteus vulgaris* (3%). Out of 37 positive patients 15 cases were positive for infant which is 41 % of total and the highest number of positive patients was infant and meropenem is most effective drug against all pathogens. The study shows the prevalence of common bacterial pathogens causing BSI and their susceptibility patterns. Such studies provide benefits of instantaneous choice of antibiotic therapy aiming at improved patient management and reduced drug resistance.

Keyword: Bacteremia, BSI, Drug resistance*, S. aureus*

INTRODUCTION

Bloodstream infections (BSIs), which include bacteremia when the infections are bacterial and fungemia when the infections are fungal, are infections present in the blood (Viscoli, 2016). Blood is normally a sterile environment (Ochei et al., 2000), so the detection of microbes in the blood (most commonly accomplished by blood cultures) is always abnormal. A bloodstream infection is different from sepsis, which is the host response to bacteria (Fan et al., 2016). Bacteremia is associated with increased morbidity and mortality (Seifert, 2009). Efforts to decrease mortality rates in children under the age of 5 years, as targeted in the United Nations Millennium Development Goal 4, have been more successful in reducing the death rate in older children than in neonates. In 2010, deaths in the neonatal period contributed 40% and 52% of mortality rates in children under the age of 5 years worldwide and in Southeast Asia, respectively (Liu et al., 2000). As more than one-third of neonatal mortality is attributable to severe infections, many deaths might be avoided by enhanced interventions to reduce the incidence of neonatal sepsis and improve access to appropriate antibiotic treatment (Saugstand, 2010).

Staphylococcus aureus is a leading cause of bacteremia, yet there remains a significant knowledge gap in the identification of relevant biomarkers that predict clinical outcomes. Heterogeneity in the host response to invasive S. aureus infection suggests that specific biomarker signatures could be utilized to differentiate patients prone to severe disease, thereby facilitating earlier implementation of more aggressive therapies (Guimaraes et al., 2019). Despite many advances in patient care, bloodstream infections (BSI) remain important causes of morbidity and mortality in hospitals especially in developing countries like India. These are among top 10 leading causes of death worldwide and most significant challenges in critical care. Laboratory confirmed BSI (LCBSI) have been classified into community acquired or hospital acquired/healthcare associated; of which, the latter is of particular concern, as the patient acquires BSI during the course of receiving treatment for other conditions within a healthcare setting. Among the other healthcare associated infections, which mainly include urinary tract infections, surgical site infections, and lung infections; BSI constitute for about 14% and are one of the leading causes of death globally (Digiovine et al., 1999). *Staphylococcus aureus* is a common cause of bacteremia and the leading cause of infective endocarditis (IE) in the industrialized world (Tong et al., 2015; Asgeirsson et al., 2018).

MATERIALS AND METHOD

Study area

This study was carried out in the Department of Microbiology of Brahmanbaria Medical College over a period (May, 2020 to April 2021). This is a very well recognized and governmentally approved 400 beds hospital in District of Brahmanbaria under the city of Chittagong where all the patients were registered by their personal information according to the rules of the organization. The sample collection, data processing, and laboratory experiment of this hospital maintained all the ethical protocol.

Sample collection

Collected blood samples were directly inoculated into adults (more than 12 years) and pediatric (Up to 12 years) FAN blood culture bottles. Bottles were incubated in the BACT/Alert machine for up to 5 days .Positive culture samples were directly inoculated on Macconkey agar and Blood agar (5% sheep blood) plates. Bacterial pathogens were identified using standard bacteriological procedure.

Identification of pathogenic microbes

For the identification procedures were applied such as gram staining ,Morphological identification and biochemical test (Parveen and Rahim, 2017; Rahman et al., 2004; Sultana et al., 2019). Isolated colonies from Macconkey agar media and blood agar media were processed for gram staining by following the steps (Primary stain-Crystal violet, Mordanting – Grams iodine, Dicolorizer-Acetone, Counterstain-Safranin). After the staining colonies of different isolated microorganisms were observed under the microscope and identified (Zinnat et al., 2011). Finally the standard biochemical test which includes Catalase, Coagulase, Indole, Urease, Oxidase, Citrate test aimed at identifying the bacterial isolate.

Antimicrobial susceptibility testing

All the isolates were tested for antibiotic susceptibility against 17 antimicrobial drugs by disc diffusion assay on Mueller-Hinton agar (Difco, Detroil, MI) with antibiotic discs (Neo-sensitabs, Rosco, Denmark) according to the modified Kirby-Bauer method. In 1972, six years after its introduction, the Kirby-Bauer method was widely adopted by clinical laboratories. Multiple authors (Bartlett, 1971; Blazevic et al., 1972; Esser and Elefson, 1970; Kenneth et al., 1970), have attested to its great reproducibility and relative simplicity. All authors have emphasized the need to follow the technique as described and to accept modifications only after full documentation of the effects of any such changes on inhibition zone diameters. The susceptibility of the bacterial isolate to each antibiotic can then be semi-quantified by comparing the size of these zones of inhibition to databases of information on known antibiotic-susceptible, moderately susceptible and resistant bacteria. In this way, it is possible to identify the most appropriate antibiotic for treating a patient's infection (Brown and Kothari, 1975).

A single colony of each isolate was inoculated into 2 ml mueller –hinton broth and incubated at 37°c for 24 hours. The culture turbidity was adjusted to 0.5McFarland standard. Sterile cotton swabs were dipped into the suspensions and spread evenly over the entire surface of Muller-Hinton agar. Antibiotic discs of appropriate concentration were placed aseptically over the surface at appropriate spatial distance of 5mm.Plates were then inverted & incubated at 37°c After 24 hours plates were examined and the diameters of the zones of inhibition were measured and interpreted as susceptible intermediate and resistant (Rahman et al., 2004).

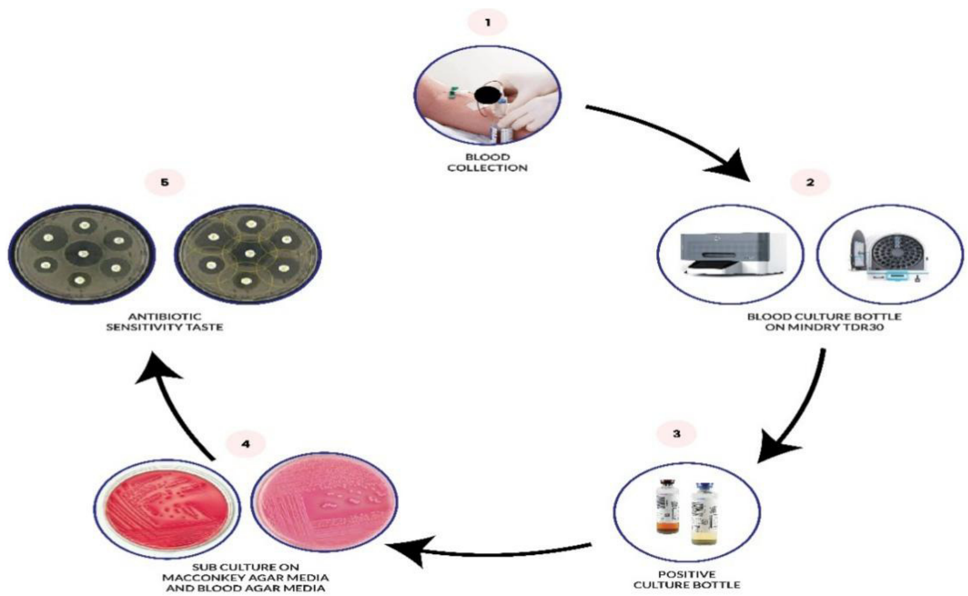

Figure 1. Procedure of blood Culture and Sensitivity test

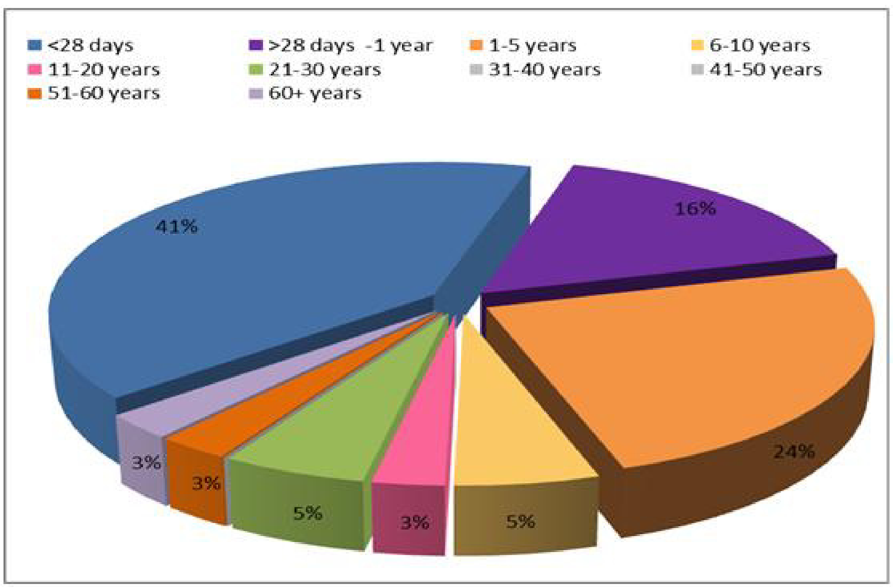

Figure 2. Pie chart showing the percentage of total isolation among the different ages .

Table 1. Results of Blood culture (n=215)

Test report	Frequency	Percentage (%)
Negative cases	178	83
Positive cases	37	17
Total cases	215	100

RESULT

After performing the cultural and microscopic observation the existence of pathogens in blood sample were determined as *Staphylococcus aureus* (51 %), *Enterococcus faecalis (*16 %) *Escherichia coli* (11%), *Klebsiella pneumoniae (8 %),* Enterobacter spp (5%), *Pseudomonas aeruginosa* (6%), *Proteus vulgaris* (3%) (Figure 3). Further confirmation of the isolates were recognized according to the results of different

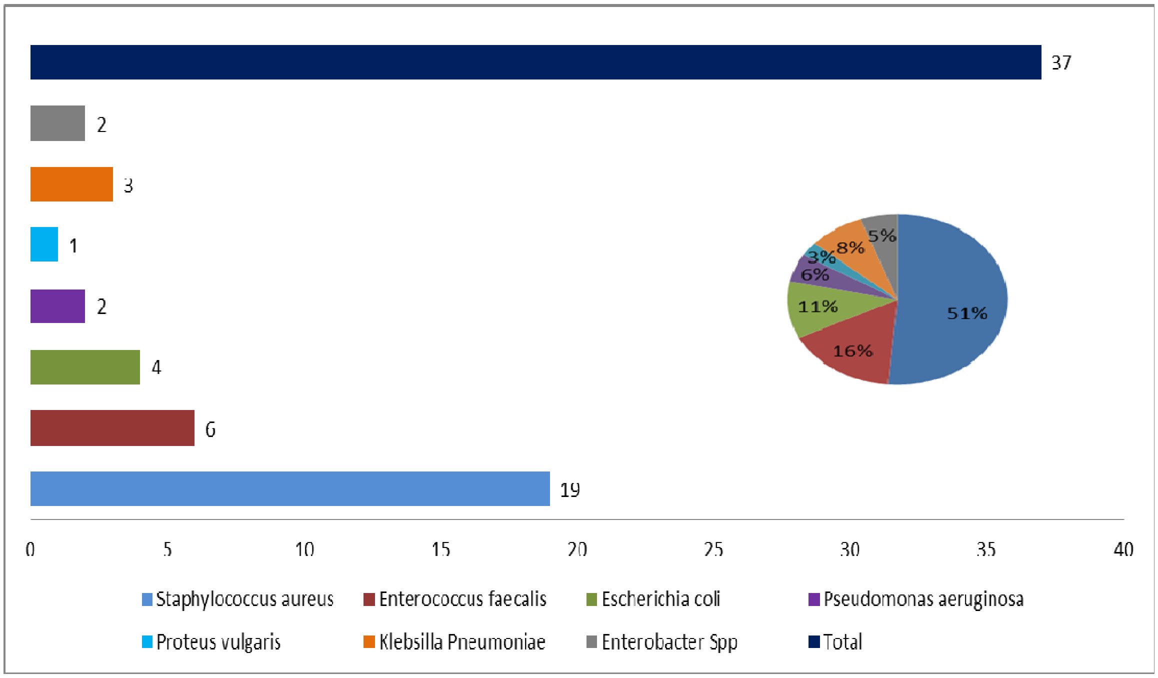

Figure 3. The bar diagram showing the frequency distribution of blood culture Isolation. Different organism among the positive cases and pie chart showing the percentage of total isolation

Table 2. Morphologically and Biochemical test results of the isolated pathogens

Isolated pathogens	Microscopic observation					Biochemical test										
						TSI				MIU						
	Gram-Staining result	Cell color	Cell shape	Cell arrangement	Lactose Fermentation	Slant	Butt	H2S	Gas	Motility	Indole	Urease	Oxidase	Citrate	Catalase	Coagulase
Escherichia coli	Gram negative	pink	Rod	Single	+	Y	Y	-	+/-	+	+	-	-	-	+	-
Enterobacter spp	Gram negative	Pink	Rod	Single	+	Y	Y	-	+	+	-	-	-	+	+	-
Proteus vulgaris	Gram negative	Pink	Rod	Swarm	-	Y	R	+	-	+	+	+	-	-	+	-
Pseudomonas aeruginosa	Gram negative	Pink	Rod	Single	-	R	R	-	-	+	-	Slow	+	+	+	-
Klebsiella pneumoniae	Gram negative	Pink	Rod	Single	+	R	Y	-	+	-	-	Slow	-	+	+	-
Staphylococcus aureus	Gram positive	Purple	Cocci	Cluster	+	Y	Y	-		-	-	+	-	+	+	+
Enterococcus faecalis	Gram positive	Purple	Cocci	Chain	+	Y	Y	-	-	-		-	-	-	-	Not done

biochemical tests (Table 3).

According to this research (Table 1) 37(17.21%) positive cases were found among 215 total blood samples. Out of 37 positive patients 15 cases were positive for infants which is 41% of total and the highest number of positive patients was infants. (Figure 3)

A total of 17 antibiotics were used against the isolated pathogens as it can be seen from (Table 3). 90% of *Staphylococcus aureus* were sensitive to Gentamicin, 79% to Meropenem, 74% Amikacine, 63% Nitrofurantoin, 74 % Amoxiclave, 63 % Linezolid, 47% Doxycycline, 16% to Azithromycine, Ceftriaxone, Penicillin, 12% to Cotri-

Table 3. Antibiotic susceptibility Test of isolated pathogens

Antibiotic	**Staphylococcus aureus**		***Enterococcus faecalis***		***Pseudomonas aeruginosa***		***Escherichia coli***		***Klebsiella Pneumoniae***		***Proteus vulgaris***		**Enterobacter Spp**	
	Total number of antibiotic	**Number of sensitive cases**	**Total number of antibiotic**	**Number of sensitive cases**	**Total number of antibiotic**	**Number of sensitive cases**	**Total number of antibiotic**	**Number of sensitive cases**	**Total number of antibiotic**	**Number of sensitive cases**	**Total number of antibiotic**	**Number of sensitive cases**	**Total number of antibiotic**	**Number of sensitive cases**
Meropenem(10 µg)	19	15(79 %)	06	04(67%)	02	02(100%)	04	04(100%)	02	02(100%)	01	01(100%)	02	02(100%)
Amikacin(30µg)	19	14(74 %)	06	05(84%)	02	01(50%)	04	03(75%)	02	01(50%)	01	01(100%)	02	01(50%)
Gentamicin(10 µg)	19	17(90 %)	06	05(84%)	02	01(50%)	04	03(75%)	02	01(50%)	01	01(100%)	02	01(50%)
Amoxiclav(30 µg)	19	14 (74%)	06	04(67%)	02	01(50%)	04	03(75%)	02	01(50%)	01	00(00%)	02	01(50%)
Nitrofurantoin(300 µg)	19	12 (63%)	06	05(84%)	02	01(50%)	04	02(50%)	02	01(50%)	01	00(00%)	02	01(50%)
Ciprofloxacin(05µg)	19	08 (42 %)	06	04(67%)	02	00(00%)	04	01(25%)	02	00(00%)	01	00(00%)	02	00(00%)
Levofloxacin(05µg)	19	06 (32%)	06	03 (50%)	02	00(00%)	04	01(25%)	02	00(00%)	01	00(00%)	02	00(00%)
Azithromycin(15 µg)	19	03 (16%)	06	02 (34%)	02	00(00%)	04	00(00%)	02	00(00%)	01	00(00%)	02	00(00%)
Doxycycline(30 µg)	19	09 (47%)	06	02(34%)	02	00(00%)	04	01(25%)	02	00(00%)	01	00(00%)	02	00(00%)
Cefuroxime (30 µg)01	19	02 (11 %)	06	01(17%)	02	00(00%)	04	00(00%)	02	00(00%)	01	00(00%)	02	00(00%)
Cefixime(05 µg)	19	00 (00%)	06	00(00%)	02	00(00%)	04	00(00%)	02	00(00%)	01	00(00%)	02	00(00%)
Ceftazidime(30 µg)	19	00 (00%)	06	00(00%)	02	00(00%)	04	00(00%)	02	00(00%)	01	00(00%)	02	00(00%)
Linezolid(30µg)	19	12 (63%)	06	04(67%)	02	00(00%)	04	01(25%)	02	00(00%)	01	00(00%)	02	00(00%)
Cotrimoxazole(25µg)	19	02 (11%)	06	01(17%)	02	00(00%)	04	00(00%)	02	00(00%)	01	00(00%)	02	00(00%)
Ceftriaxone (30 µg)	19	03(16 %)	06	01(17%)	02	00(00%)	04	01(25%)	02	00(00%)	01	00(00%)	02	00(00%)
Amoxicillin (10 µg)	19	00 (00%)	06	00(00%)	02	00(00%)	04	00(00%)	02	00(00%)	01	00(00%)	02	00(00%)
Penicillin	19	03 (16%)	06	01(17%)	Not done	Not done	Not done	Not done	Not done	Not done	Not done	Not done	Not done	Not done

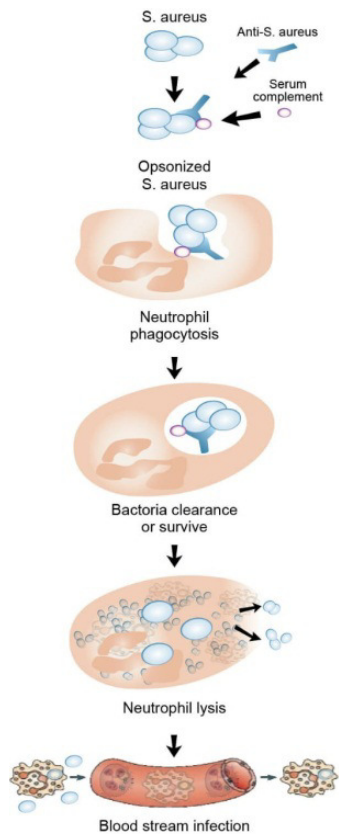

Figure 4. The figure showing neutrophil-mediated phagocytosis

moxazole,10% to levofloxacin, 9% to Levofloxacin. 84% of Enterococcus spp are sensitive to Gentamicin, Amikacin and 67% to Meropenem.100% *Escherichia coli* were sensitive to Meropenem,75% sensitive to Gentamicin, Amikacine, Amoxiclave and 50% to Nitrofurantoin. 100% *Klebsiella pneumoniae, Pseudomonas aeruginosa*, Enterobacter spp were sensitive to Meropenem, 50% sensitive to Gentamicin, Amikacine, Amoxiclave and Nitrofurantoin. 100% *Proteus vulgaris* were sensitive to Meropenem, Gentamicin, Amikacine. All pathogens are resistant to Amoxicillin, Ceftazidine, Cifixime.

DISCUSSION

This literature review provides a comprehensive analysis on the AMR pattern of bacterial BSI in the pediatric population of Bangladesh. This study found higher reports of bacteremia caused by Gram-positive bacteria (67.57%) {S*taphylococcus aureus* (51.35 %), *Enterococcus faecalis (*16.62%)} compared with Gram-Negative bacteria (32.43%) [*Escherichia coli* (10.81%), *Klebsiella pneumoniae (8.10%),* Enterobacter spp (5.41%), *Pseudomonas aeruginosa* (5.41%), *Proteus vulgaris* (2.70%)]. In south Asia gram-negative bacilli (*Escherichia coli*, *Klebsiella* spp., *Pseudomonas* spp., *Acinetobacter* spp.) and gram-positive cocci (such as *Staphylococcus aureus* and *Staphylococcus epidermidis*) are important causes of septicemia (Tanver and Zaidi, 2009; Kasistha et al., 2009).

According to this research (Table 1) 37 (17.21%) positive cases were found among 215 total blood samples. On other hand four hundred fifty-five positive blood culture results, Gram-positive organisms accounted for 80% (366/455) of the positive culture results, Gram-negative organisms accounted for 11% (48/455), and yeast for 9% (41/455) (James and Biemer, 1973). Gram negative 58.5% predominated over Gram positive cocci 41.5% (Blazevic et al., 1972). Those are imparity with our findings.

According to this research out of 37 positive patients 15 cases were positive for infants which is 41 % of total and the highest number of positive patients was infants. Out of 3064 suspected cases of septicemia 588(19.2%) were positive for bacterial isolates. There were 379(64.5%) isolates from early onset less than or equal 7 days septicemia cases, while 209 (35.5%) were from onset age more than 7 days (Agnihotri et al., 2004). This is not similar to our research.

From January 2005 to December 2014, a total of 103,679 blood samples were received from both hospitalized and domiciliary patients and among them 14015 samples were found to be culture positive, that is 13.52%. Over these past ten years 11.9, 12.2, 13.9, 16.5, 16.0, 17.3, 12.7, 12.9, 10.7 and 11.9% of the samples were found to be culture positive respectively (Ahmed et al., 2017). Those are similar to our findings. Need continue writing the one or two digits after the decimal number.

We found in our research Blood stream infection in neonate positivity rate 41% that is similar to positivity rate 36% (Hossain et al., 2004). In a study done in India, it has a similar rate of positivity 16-54% (Tanver and Zaidi, 2009; Kasistha et al., 2009; Shitaye et al., 2010; Giulia De Angelis et al., 2019).

In this research, *Staphylococcus aureus* showed 90% sensitive to Gentamicin, Enterococcus spp showed that 84% was sensitive to Gentamicin, Amikacin, 100% *Escherichia coli,* Enterobacter spp were sensitive to Meropenem that is similar with (Giulia De Angelis et al., 2019)*, Klebsiella pneumoniae, Pseudomonas aeruginosa* also 100% sensitive to Meropenem that is not similar with (Giulia De Angelis et al., 2019). 100% *Proteus vulgaris* were sensitive to Meropenem, Gentamicin, Amikacine. All pathogens are resistant to Amoxicillin, Ceftazidine, Cifixime.

In our research we use 17 antibiotic Meropenem, Gentamicin, Amikacin, Linezolid, Amoxiciclave are more effective other are more to minor resistant.

Staphylococcus aureus enter the Bloodstream by defecting neutrophils

Staphylococcus aureus is a human commensal but also a common course of serious infections, ranging from mild skin infections to more serious life-threatening wound and bloodstream infections (Lowy, 1998). The innate immunity is an important part of the host defense in elimination of infections caused by *S. aureus*. Notably, many virulence factors of *S. aureus* are directed toward elements of the innate immune defense including its principal phagocyte, the neutrophil (Rigby and DeLeo, 2012; Spaan et al., 2013).

For neutrophils, initiation of phagocytosis requires decoration of bacteria with opsonins that are recognized by specific surface receptors. Igs and complement components are the predominant factor in serum that enables efficient opsonization.

The attributed role of opsonins in neutrophil-mediated phagocytosis may, however, be dependent on the methodology, related to the site of infection. A recent example (Lu et al., 2014) showed that phagocytosis of *S. aureus* by human neutrophils in suspension depends on opsonization, while adherent neutrophils internalize more bacteria independent of opsonization.

The actual phagocytosis process can be distinguished in several phases: (1) attachment of the opsonized particle upon recognition by specific receptors, (2) pseudopod extensions around attached particle whereby it is still exposed to the environment (“zippering”), and (3) completion of the engulfment resulting in the formation of a phagosome, which is an outside-in compartment inside the cell . The next steps involve mobilization and fusion of the phagosome with different granule types resulting in the liberation of granule content that is required for killing of the microorganism (Flannagan et al., 2012; Nordenfelt and Tapper, 2011). Staphylococci can survive within the phagosome and have developed several ways to escape neutrophil killing. For invading staphylococci, phagocytosis and killing by human neutrophils is the biggest threat. Figure 4

CONCLUSION

Staphylococcus aureus, *Enterococcus faecalis and Escherichia coli* were the leading causes of neonatal septicemia in our study. These bacteria isolates were highly resistant to Amoxicillin, which is considered a third generation or aminopenicillin and Third-Generation Cephalosporins (cefixime, ceftazidime). New generation carbapenem (Meropanam) highly effective against isolated bacteria, Drug of Aminoglycoside group also effective (Amikacin and Gentamicine). First generation Quinolone Ciprofloxacin and Second generation Quinolone Levofloaxacine a little effective. Due to the improper therapeutic treatments and incomplete medication, overuse of antibiotics - some pathogens become resistant against the previously used antibiotics over time. Regular and exact diagnosis is needed to minimize the risk of increasing drug resistance which would help the patients physically and financially. Development of alternative drugs is necessary for such conditions and patients should be advised properly to take the antibiotic medication to control the condition of rapidly occurring resistance traits

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