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ORIGINAL ARTICLE

Gram negative organisms isolated from Blood Cultures and their Susceptibility Pattern in a Tertiary Care Hospital

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ABSTRACT

Background: Bloodstream infections (BSIs) are an important frequent health problem in terms of their high incidence and lethal outcomes. The bacteria that frequently cause bacteremia are Staphylococcus, Streptococcus, Enterococcus, Escherichia coli, Klebsiella, Enterobacter, Pseudomonas, Neisseria and Haemophilus. Gram negative rods constitute a significant bulk in BSIs. The bloodstream infections due to multidrug resistant pathogens are on the rise globally making treatment more challenging.

Aim: To identify the gram negative organisms causing blood stream infections and assess their susceptibility pattern so as to provide guidance for the empirical treatment hoping for better clinical outcome.

Methodology: A retrospective, cross-sectional descriptive study carried out in Pathology Laboratory of Sharif City Hospital, Lahore. All the blood culture samples received in Microbiology laboratory between June 2017 to June 2019 were included in the study by non-probability consecutive sampling. Blood cultures were proceeded by subculturing on 1st and 5th day on MacConkey and Blood agar. The colonies obtained were identified through gram staining and biochemical profile. API20E was used for Enterobacteriaceae. Antibiotic susceptibility testing of the pathogens was by Kirby Bauer disc diffusion method.

Results: In the current study 663 blood cultures were analyzed. Only 11.9% exhibited positive microbial growth. 55.7% of the positive cultures revealed gram negative bacteria. Among the pathogens isolated, *E.coli* was found to be responsible for BSIs in 22.7% cases, followed by *Salmonella Typhi* 20.4% and *Klebsiella pneumoniae* 18.1%.The gram negative rods exhibited a very high resistance for penicillins, cephalosporins and fluoroquinolones. The efficacy of aminoglycosides and results for carbapenems susceptibility were hopeful.

Conclusion: The study shows that the Gram negative bacteria causing BSIs have shown unsatisfactory susceptibility to most of the commonly prescribed antimicrobials. The rising drug resistance has a major impact on the selection and prescription of antibiotics and calls for judicious use of antibiotics.

Keywords: Gram Negative Organisms, Blood Culture, Antimicrobial Susceptibility Pattern

INTRODUCTION

Blood is a sterile fluid. Bloodstream invasion by microorganisms is one of the most significant condition in infectious diseases[1]. Bacteremia is the presence of microorganisms in the blood whereas sepsis is a life-threatening condition with bacteremia and systemic manifestations. The pathogens produce toxins into the bloodstream leading to the release of cytokines. The patient presents with high grade fever, chills, tachycardia, tachypnoea and hypotension[2,3]. It can also lead to septic shock, disseminated intravascular coagulation and multi-organ failure[4]. The detection of viable bacteria in blood cultures in which the contamination has been excluded is labelled as bloodstream infection[5]. The bloodstream infections (BSIs) can be classified as hospital onset and community onset. The hospital onset BSI occur more than 48 hours after hospital admission whereas community onset BSI occur less than 48 hours after hospital admission[6].

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Bloodstream infections (BSI) are an important frequent health problem in terms of their high incidence and lethal outcomes. These infections are causative for morbidity, mortality and financial cost worldwide[7,8]. About 13.5 million cases of sepsis occur on a global scale every year[3]. Bloodstream infections can be life-threatening in patients of intensive care units (ICUs). The mortality rate of bloodstream infections ranges between 35-50%[9]. It has been reported that bloodstream infections and the associated septic shock is responsible for 6% and 3% of all ICU admissions with 40% and 49% in-hospital mortality respectively in the developed world[10]. Blood culture is one of the most frequently performed microbiological test in hospitals worldwide and still remains the gold standard for detecting bloodstream infections.[11] Antimicrobial susceptibility testing is a vital prerequisite for treating bloodstream infections[8]. Early detection, identification plus antimicrobial therapy nevertheless improves patient condition and reduces the development of antibiotic resistance[11].

The bacteria that frequently cause bacteremia are Staphylococcus, Streptococcus, Enterococcus, Escherichia

coli, Klebsiella, Enterobacter, Pseudomonas, Neisseria and Haemophilus[5]. The epidemiology of the causative agents is not static and constantly changing over time. The management of BSI is further complicated especially in resource limiting settings with organisms from blood cultures and antibiotic sensitivity pattern having a crucial epidemiological role in a geographic locale plus assisting physicians in determining primary antimicrobial agents[12]. The bloodstream infections that are caused by pathogens that have now gained multidrug resistance are globally on the rise making treatment more difficult[13]. In healthcare clinics plus hospitals, infections that are being caused by multidrug resistant microbes is becoming challenging causing long-term hospitalization of patients and increasing mortality rate. This also increases the risk of other infections putting a burden on the cost of healthcare system[12]. Such a rise in antibiotic resistance is a global concern that can differ according to the varying geographic regions plus epidemiological features[14]. Combating the antimicrobial resistance is a global challenge especially in the developing countries. Antimicrobial resistance occurs due to genetic mutations and inappropriate antimicrobial selection for treatment[13]. Knowledge of resistance and sensitivity patterns can assist healthcare workers in defining better drug regimes and make better decisions based on the approach to solve the problems of antimicrobial resistance[14].

The current study was designed for identification of gram negative organisms causing infections of the bloodstream plus their antimicrobial susceptibility pattern. There is a minimum turnaround time of 2-3 days in getting the results of blood culture report. The empirical antibiotic therapy is usually initiated in suspected cases of sepsis. But for that purpose, the clinicians must know about the antimicrobial resistance pattern of common pathogens causing sepsis. The prevalence of causative organisms of sepsis differs from region to region[15]. The surveillance of pathogens isolated from blood cultures in a hospital will help in determining the organisms causing bloodstream infections in different clinical disciplines. It will also provide data for empirical antimicrobial therapy and warn the clinicians about the emerging pathogens[16].

The objective of the study was to detect gram negative rods isolated from blood cultures and their antimicrobial susceptibility pattern in Sharif City Hospital, Lahore.

METHODOLOGY

This study was conducted in the Pathology Laboratory of Sharif City Hospital, Lahore from June 2017 to June 2019. All the blood culture samples received in Microbiology section were included in the study by non-probability consecutive sampling.

The blood samples were received in blood culture bottles containing tryptic soya broth and polyanethol sulphonate. The bottles were placed in the incubator at 35°C for 5 days. First subculture was performed on MacConkey and blood agar after 48 hours. The first culture being negative, was followed by second subculture on blood agar and MacConkey agar in the following 72 hours. If no growth was obtained after 2 subcultures, the final report of negative blood culture was issued after 5 days. In the case of positive first or second subculture, the isolated organism was identified by colony morphology, gram staining and biochemical tests. The gram negative bacteria were identified by using analytical profile index (API). Direct gram staining from blood culture bottles plus re-culture of specimens was done to confirm the presence of a causative pathogen. Antibiotic susceptibility testing of causative microbes was done by Kirby Bauer disc diffusion method. The suspension of the causative organism was prepared by mixing 3-4 colonies of the organism in normal saline and matched with 0.5 McFarland turbidity standard. This was followed by evenly applying suspension on Mueller-Hinton agar plates using a sterile swab. The antibiotic discs were then placed on plates following an aseptic technique. These plates were finally incubated at 35°C for 18-24 hours. Zone diameters of different antibiotics were then studied in accordance to the Clinical & Laboratory Standards Institute (CLSI) 2019. The antibiotics applied have been in 3 categories: susceptible, resistant, or intermediate. The antibiotic panel applied for gram negative bacteria included ampicillin, co-amoxiclav, ceftazidime, cefotaxime, ceftriaxone, cefepime, imipenem, meropenem, tazobactam-piperacillin, amikacin and ciprofloxacin, co-trimoxazole, chloremphenicol (for *S.Typhi)* and doxycycline (for *acinetobacter sp).*

Statistical analysis: SPSS version 25.0 was employed for analyzing the data of this study. Age factor of patients was expressed as mean and standard deviation. Department, gender, prevalence of positive blood cultures plus antibiotic susceptibility pattern of isolates were expressed as percentage and frequency.

RESULTS

Table-1 identifies that among 79 organisms, 44(55.7%) were gram negative rods and 25 (31.6%) were gram positive cocci while 10(12.7%) were Candida.

Table-2 demonstrates that among 44 gram negative rods, 3(6.8%) were *Serratia spp.*, 9(20.5%) *Salmonella Typhi*, 7(15.9%) *Pseudomonas aeruginosa*, 8(18.2%) *Klebsiella spp.*, 10(22.7%) *E. coli* and 7(15.9%) were *Acinetobacter spp*.

Table-3 exhibits that among 44 patients with gram negative rods, 28(63.6%) were upto 10 years old, 11(25%) were 11-30 years old and 5 (11.4%) patients were more than 30 years old. The mean age of the patients was 12.04±15.72 years.

Table-4 claries that among 44 patients with gram negative rods, 33(75%) were males and 11(25%) were females.

Table-5 showed the susceptibility of gram negative rods to drugs and found that 59.1% GNRs were sensitive to MEM followed by IPM (54.5%), TZP (34.3%), SXT (29.7%), AK (28.6%), CN (28.6%), CIP (25%), FEP (22.7%), CRO (21.6%), ATM (20%), AMC (19%), CTX (18.9%), CAZ (18.2%), LEV (17.1%), CE (16.7%), CXM (14.3%), AMP & AML (9.1%) . Among these GNRs, 14.3% GNRs were found intermediate to FEP (18.2%), 11.4% each to AK, CN, MEM, IPM and CIP, followed by CAZ (6.8%), SXT (5.4%) and 2.7% each to CRO and CTX. A very high resistance was observed for AML & AMP (90.9%) followed by CXM

(85.7%), CE (83.3%), AMC (81%), CTX (78.4%), CRO (75.7%), CAZ (75%), TZP (65.7%), SXT (64.9%), CIP (63.6%), 60% each to AK and CN, FEP (59.1%), IPM (34.1%) and MEM (29.5%).

Table-1: Frequency of organisms isolated

Organisms	No.	%age
Gram negative rods	44	55.7
Gram positive cocci	25	31.6
Candida	10	12.7

Table 2: Frequency of gram negative pathogens

Organisms	No.	%age
Serratia spp.	3	6.8
Salmonella Typhi	9	20.5
Pseudomonas aeruginosa	7	15.9
Klebsiella spp.	8	18.2
E. coli	10	22.7
Acinetobacter spp	7	15.9
Total	44	100.0

Table-3: Frequency of gram-negative pathogens according to age group

Age	No.	%age
Upto 10 years	28	63.6
11-30 years	11	25.0
Above 30 years	5	11.4
Mean±SD	12.04±15.72	

Table-4: Frequency of gram negative rods according to gender

Gender	n	%age
Male	33	75.0
Female	11	25.0
Total	44	100.0

Figure-1: Frequency of gram negative rods according to age group

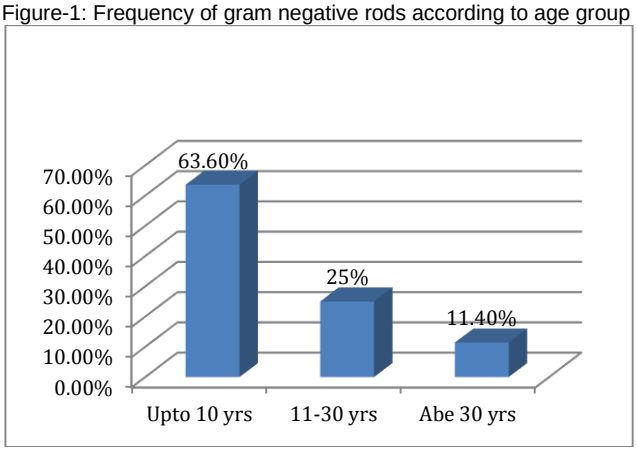

Figure-2: Frequency of gram negative rods according to gender

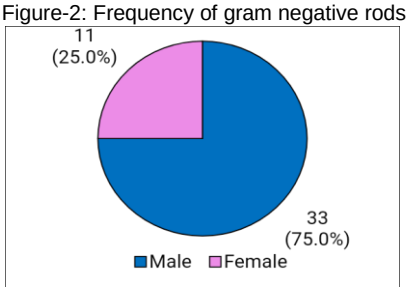

Table-5: Gram negative rods sensitivity to drugs

Drugs	*Serratia sp*			*Salmonella Typhi*			*Pseudomonas aeruginosa*			*Klebsiella pneumoniae*			*E. coli*			*Acinetobactersp*			Percentages (%)		
	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R
AK			3				1	2	4	4	2	2	5		5			7	28.6	11.4	60.0
AMC			3							1		7	3		7				19.0	0.0	81.0
AML			3									8			10				0	0.0	100
AMP			3	2		7						8			10				9.1	0.0	90.9
ATM			3				2		5										20.0	0.0	80.0
CAZ			3				2		5	1		7	1	2	7		1	6	18.2	6.8	75.0
C				2		7													22.2		77.8
CIP			3	4		5	1		6	2	2	4	3	2	5		1	6	25.0	11.4	63.6
CN			3				1	2	4	4	2	2	5		5			7	28.6	11.4	60.0
CRO			3	4		5				1		7	3		7		1	6	21.6	2.7	75.7
CTX			3									8	3		7		1	6	18.9	2.7	78.4
CXM			3									8	3		7				14.3	0.0	85.7
FEP			3				1	1	5		2	6	3	3	4		2	5	22.7	18.2	59.1
IPM	1	1	1	7		2	3		4	5	2	1	8		2		2	5	54.5	11.4	34.1
MEM	1	1	1	9			3		4	5	2	1	8		2		2	5	59.1	11.4	29.5
SXT	2		1	2		7				2		6	2	2	6	1		6	29.7	5.4	64.9
TZP			3				2		5	3		5	7		3			7	34.3	0.0	65.7
DO																3		4	42.8		57.2

DISCUSSION

Blood stream infections (BSIs) are among the major causes of mortality in patients of all age groups. The situation gets worse with the rising antimicrobial drug resistance among bacteria particularly gram negative rods. This has led not only to infections being hard to manage but also untreatable infections as evident by the therapeutic failures. Gram negative rods constitute a significant bulk in BSIs. This study aimed to isolate the gram negative rods causing blood stream infections and assess their susceptibility pattern so as to revise the empirical treatment regime hoping for better clinical outcome.

In the current study 663 blood cultures received in Microbiology laboratory SMCH, from the patients showing signs and symptoms of septicemia were analyzed. Out of these 88.1% turned out to be negative and only 11.9% exhibited positive microbial growth. 55.7% of the positive cultures revealed gram negative bacteria showing that gram negative bugs are major pathogens for blood stream

infections. However, 31.6% were gram positive cocci and 12.7% were candida species. These findings are concordant with a systematic review showing overall percentage of 19.1% positive blood cultures in Africa and 28.0% in Asia respectively. Similar to our study gram-negative bacteria were more prevalent and were isolated in 63.9% and gram-positive bacteria in 35.8% cases.[17]

As for as the age group is concerned, current study showed that 28(63.6%) patients were up to 10 years old, 11 (25.0%) were 11-30 years old and 5 (11.4%) were more than 30 years old. Our results are in agreement to another study evaluating the trends of BSIs in Pediatric and adult population. This study exhibited that BSIs were more common in pediatric patients (9.3%) than in adult patients (6.6%), particularly the highest proportion was found in infants (12.9%).[18] Among the pathogens isolated, *E.coli* was found to be responsible for BSI in 22.7% cases , followed by *Salmonella typhi* 20.4%. and *Klebsiella pneumoniae* 18.1%. These results do not conform to the findings of a study in Nepal showing *Salmonella* Typhi as the commonest pathogen isolated in 71% cases of bloodstream infections, followed by *Salmonella* paratyphi A as the second common bug being isolated in 16% cultures. *Escherichia coli* was found in 5% and *Klebsiella pneumonia* in 0.5% cultures respectively[19].

However, our results are consistent with Sentry Antimicrobial Surveillance Program that concluded that among GNR, *E.coli* is the major etiological agent for Blood stream infections*. Escherichia coli* was obtained in 20.5%, followed *by Klebsiella pneumonia* (7.7%)[20]. In current study, non-fermentor gram negative bacilli (NFGNB) were the etiological agents in 34.1% cases. These findings are consistent with an Indian study that yielded NFGNB in 32.7% blood cultures. However, in our study *Pseudomonas aeruginosa* and *Acinetobacter sp.* were isolated in 15.9% cases each and only one isolate (2.2%) of *Stenotrophomonas maltophila* was isolated. These results differ from various Indian studies where *Acinetobacter boumannii* was the most common organism, followed by *Strenotrophomonas maltophilia*, and *Pseudomonas aeruginosa*[21,22].

Present study shows that majority of the patients suffering from GNR Septicemia were males as 33 males and 11 females exhibited Gram negative bacteria in their blood cultures. Our findings are similar to a cohort study that showed men were at higher risk for bloodstream and surgical site infections than women. This predisposition might be because of heavier skin colonization in males at the insertion site of Central venous catheter and coarse hair in males that impedes wound dressing and promote chances of infection[23]. The susceptibility pattern of the pathogens was also assessed using the Kirby -Bauer disc diffusion assay and it revealed resistance to majority of the first and second line antibiotics. Our results show that except for 2 isolates of *Salmonella Typhi,* all other isolates of *Enterobacteriaceae* exhibited resistance to Ampicillin. While only 3(30%) *E.coli* and 1 (12.5%) *Klebsiella pneumoniae* were sensitive to Amoxicillin-clavulanate. The findings are more or less similar to the results obtained in a research conducted in Saudi Arabia that exhibited 4.3% *E.coli* sensitive to Ampicillin. As far as Co-Amoxiclav is concerned, 19% *E.coli* and 13.1% *Klebsiella pneumoniae* were found susceptible.[24]

A second combination drug Tazobactam –piperacillin was also evaluated for its efficacy. 70% *E.coli* and 60% *Klebsiella pneumoniae* were susceptible to this drug. Similar findings were observed in other studies proving Tazobactam –pipercillin to be as good as meropenem for resistant blood stream infections[24,25].

Cephalosporins could not prove to be good therapeutic option for Gram negative bugs as 7(70%) *E.coli*, 8(80%), *Klebsiella pneumoniae*, 3 (100%) *Serratia sp*. were resistant to all the tested 3rd and 4th generation cephalosporins. Poor susceptibility pattern of cephalosporins has also been observed in other studies.[24,26] This owes to wide scale and undue use of these drugs. *Salmonella Typhi* exhibited 44.4% susceptibility to Ceftriaxone. Our study found 77.7% MDR Typhi and 55.5% XDR Typhi. Much lower incidence of MDR Typhi was observed in a 6year retrospective study conducted in Dhaka in 2014. This study isolated 20.92% MDR typhoidal *salmonella spp*.[27] Hence, the drug resistance among Typhi is on a dramatic rise, highlighting the threat of therapeutic failure and demanding judicious use of antimicrobials along with implementation of Infection control practices.

A very high resistance was observed for fluoroquinolones among the isolated pathogens. 3(30%) isolates of *E.coli* and only 2(20%) isolates of *Klebsiella pneumoniae* were found susceptible to ciprofloxacin and levofloxacin. However, none of the *Serratia spp*. isolates exhibited susceptibility to fluoroquinolones. Such a high incidence of resistance is quite alarming. This may be attributed to factors like unsupervised drug dispensing practices in the community and injudicious use of antibiotics in our hospitals. Unlike our observations, certain studies support the use of fluoroquinolones as empiric therapy for blood stream infections as evident by better therapeutic outcomes in comparison with broad spectrum beta-lactam drugs for BSIs caused by GNR[28]. Even recurrence of bacteremia was found to be much reduced with use of oral fluoroquinolones than beta-lactam drugs[29]. The reason for such difference should be sorted out and genome analysis of the strains should be conducted.

The efficacy of aminoglycosides was found to be relatively better as 50 % isolates of *E.oli* and *Klebsiella pneumoniae* were sensitive to both gentamicin and amikacin. Similarly, promising results are revealed by a study showing 90-100% susceptiblilty of bacterial isolates to amikacin[30]. The results for carbapenems suscetibiltiy were hopeful as 62.5% *Kebsiella pneumoniae*, 80% *E.coli*, 33% *Serratia sp.* were susceptible to imepenem and meropenem. Our results are concordant with another study that exhibits 88% *E.coli*, 100% *Klebsiella sp* and 50% *Citrobacter sp*. susceptible to imepenem. [31]Another study obtained only 10% *Klebsiella pneumoniae* isolates resistant to carbapenems[26].

The results for susceptibility of non-fermenting gram negative rods were quite worrisome particularly for *acinetobacter sp*. Only 1 isolate (14.2%) of *Pseudomonas aeruginosa* showed response to ciprofloxacin, levofloxacin, cefipime, gentamicin and amikacin. 2 isolates (28%) were susceptible to Tazobactam- piperacillin, ceftazidime, and

aztreonam. However, none of the *Acinetobacter spp.* isolates yielded response to any of these tested drugs giving 100% resistance to these drugs. 3 (42.8%) *Pseudomonas aeruginosa* isolates exhibited susceptible zones to meropenem and imepenem. However, *Acinetobacter sp.* showed 0% susceptibility to carbapenems too. Compared to our results, much better susceptibility has been observed in an Indian study. This study showed 90.8% and 86.7% *Pseudomonas aeruginosa* were susceptible to ertapenem and imepenem respectively. Even aminoglycoside susceptibility was found to be higher i.e. 64.02% for amikacin. *Acinetobacter spp.* isolates also exhibited satisfactory results for various tested drugs. 60% isolates were susceptible to imipenem and 48.9% to gentamicin. 21 *Acinetobacter* isolates of our study showed 42.8% sensitivity to doxycycline and 14.2% to co-trimoxazole. The observations of an Indian study are in agreement with our study showing 66.6% MDR *Acinetobacter* isolates being susceptible to doxycycline[32]. Another Egyptian study proved that the combination of Doxycycline and co-trimoxazole can be successfully used for the cure of nosocomial MDR-*Acinetobacter* infection in critically ill patients[33].

CONCLUSION

The study shows that the Gram negative bacteria causing BSIs have shown unsatisfactory susceptibility to most of the commonly prescribed antimicrobials. Whereas carbapenems and aminoglycosides showed better response. The rising drug resistance has a major impact on the selection and prescription of antibiotics and calls for judicious use of antibiotics.

Limitations: Future studies with a larger group of population and enrolling patients from different hospitals should be carried out. As this is a single centered study so it is a limitation of this study.

RECOMMENDATIONS

1. Blood culture should be performed in every suspected case of sepsis and antimicrobial susceptibility testing should be performed to prevent the problem of emerging antibiotic resistance.
2. Newer antibiotics like colistin, plazomicin should be assessed for their activity against pathogens of Blood stream infections. This might help in development of an effective empiric therapy for management of blood stream infections.

REFERENCES

1. Banik A, Bhat SH, Kumar A, Palit A, Snehaa K. Bloodstream infections and trends of antimicrobial sensitivity patterns at Port Blair. J Lab Physicians. 2018; 10(3):332-7. Available from: http://www.jlponline.org/text.asp?2018/10/3/332/236114.
2. Simkhada P, Raj KCS, Lamichhane S, Subedi S, Shrestha UT. Bacteriological profile and antibiotic susceptibility pattern of blood culture isolates from patients visiting Tertiary Care Hospital in Kathmandu, Nepal. Glob J Med Res. 2016; 16(1): 25-31.
3. Kumalo A, Kassa T, Mariam ZS, Daka D, Tadesse AH. Bacteriological profile of adult sepsis and their antimicrobial susceptibility pattern at Jimma University Specialized Hospital, South West Ethiopia. Health Sci J. 2016; 10(2:3):1-8.
4. Negussie A, Mulugeta G, Bedru A, Ali I, Shimeles D, Lema T, et al. Bacteriological profile and antimicrobial susceptibility pattern of blood culture isolates among septicemia suspected children in selected hospitals Addis Ababa, Ethiopia. Int J Biol Med Res. 2015 Nov; 6(1):4709-17.
5. Abebaw A, Tesera H, Belachew T, Mihiretie GD. The bacteriological profile and antibiotic susceptibility pattern among patients with suspected bloodstream infections, Gondar, north-west Ethiopia. Pathology and Laboratory Medicine International. 2018;10.
6. Cross A, Levine MM. Pattern of bacteremia etiology. Lancet. 2017 Oct; 17(10):1005-6. doi: https://doi.org/10.1016/S1473-3099(17)30491-7.
7. Opintan JA, Newman MJ. Prevalence of antimicrobial resistant pathogens from blood cultures: results from a laboratory based nationwide surveillance in Ghana. Antimicrob Resist Infect Control. 2017; 6:64.
8. De Angelis G, Posteraro B, Menchinelli G, Liotti FM, Spanu T, Sanguinetti M. Antibiotic susceptibility testing of pathogens isolated from blood culture: a performance comparison of Accelerate PhenoTM and Vitec® 2 systems with the broth microdilution method. J Antimicrob Chemother. 2019 Jan 1;74(1):i24-i31. doi: 10.1093/jac/dky532.
9. *Nazir A, Sana I, Peerzada BY, Farooq T.* Study of prevalence and antimicrobial susceptibility pattern of blood culture isolates from a tertiary care hospital of North India. Int J Res Med Sci. 2018 Dec; 6(12):4046-52.
10. Dat VQ, Vu HN, The HT, Nguyen HT, Hoang LB, Viet DVT, et al. Bacterial bloodstream infections in a tertiary infectious diseases hospital in Northern Vietnam: aetiology, drug resistance, and treatment outcome. BMC Infect Dis. 2017; 17: 493. doi: 10.1186/s12879-017-2582-7.
11. Hamer DH, Darmstadt GL, Carlin JB, Zaidi AK, Yeboah-Antwi K, Saha SK, et al. Etiology of bacteremia in young infants in six countries. Pediatr Infect Dis J. 2015; 34(1):e1-8.
12. Keihanian F, Saeidinia A, Abbasi K, Keihanian F. Epidemiology of antibiotic resistance of blood culture in educational hospitals in Rasht, North of Iran. Infect Drug Resist. 2018; 11:1723-8.
13. Kitila KT, Taddese BD, Tinsae K/ Hailu M, Sori LM, Geleto SE, Mengistu GZ, et al. Assessment of bacterial profile and antimicrobial resistance pattern of bacterial isolates from blood culture in Addis Ababa Regional Laboratory, Addis Ababa, Ethiopia. Clin Microbiol. 2018; 7:2. doi: 10.4172/2327-5073.1000312.
14. Zhang X, Gu B, Mei Y, Wen Y, Xia W. Increasing resistance rate to carbapenem among blood culture isolates of Klebsiella pneumoniae, Acinetobacter baumannii and Pseudomonas aeruginosa in a university-affiliated hospital in China, 2004-2011. The Journal of Antibiotics. 2014; 68(2):115-20.
15. Mohanty A, Singh TS, Kabi A, Gupta P, Gupta P, Kumar P. Bacteriological profile and antibiotic sensitivity pattern of hospitalacquired septicemia in a tertiary care hospital in North East India. Asian J Pharm Clin Res. 2017;10(11):186-9.
16. Mehdinejad M, KhosraviAD,Morvaridi A. Study of prevalence and antimicobial susceptibility pattern of bacteria isolated from blood cultures. J Biol Sci. 2009; 9(3):249-53.
17. Droz, N, Hsia, Y, Ellis, S. et al. Bacterial pathogens and resistance causing community acquired paediatric bloodstream infections in low- and middle-income countries: a systematic review and meta-analysis. Antimicrob Resist Infect Control .2019; 8: 207. https://doi.org/10.1186/s13756-019-0673-5
18. Parajuli NP, Parajuli H, Pandit R, Shakya J, Khanal PR. Evaluating the Trends of Bloodstream Infections among Pediatric and Adult Patients at a Teaching Hospital of Kathmandu, Nepal: Role of Drug Resistant Pathogens. Can J

Infect Dis Med Microbiol. 2017; 2017:8763135. doi:10.1155/2017/8763135
19. Bhandari P, Manandhar S, Shrestha B, &Dulal N. Etiology of bloodstream infection and antibiotic susceptibility pattern of the isolates. Asian Journal of Medical Sciences. 2015; 7(2): 71-75. https://doi.org/10.3126/ajms.v7i2.13444
20. Daniel J ,Diekema DJ, Hsueh PR, Mendes RE, Pfaller MA, Rolston KV, Sader HS, Jones RN. The microbiology of bloodstream infection: 20-year trends from the SENTRY antimicrobial surveillance program. Antimicrob Agents Chemother.2019; 63 (7) : 1-10. e 00355-19. https://doi .org/10.1128/AAC.00355-
21. Chaudhury N, Paul R ,Misra R N , Subhra SC , Mirza S and Sen S. Evaluating the Trends of Bloodstream Infections by Nonfermenting Gram Negative Bacilli among the Patients in a Tertiary Care Hospital of Western Part of India and its Antibiogram . Int.J.Curr.Microbiol.App.Sci .2019; 8(1): 1149-1162
22. Nazir A, Peerzada B Y, Nazir I S et al. Spectrum of non-fermenting gram negative bacilli isolated from patients with blood stream infections in a tertiary care hospital in North India. Int J Res Med Sci. 2019 May; 7(5):1762-1766
23. Cohen B, Choi Y J, , Hyman S,, Furuya E Y, Neidell M, Larson E. Gender Differences in Risk of Bloodstream and Surgical Site Infections. J Gen InterN Med. 2013 Oct; 28(10): 1318–1325.
24. Bandy A, Almaeen A H. Pathogenic spectrum of blood stream infections and resistance pattern in Gram-negative bacteria from Aljouf region of Saudi Arabia. PLOS ONE. June 9, 2020;15(6): e0233704 https://doi.org/10.1371/journal.pone.0233704
25. Harris PNA, Tambyah PA, Lye DC, et al. Effect of piperacillin-tazobactam vs meropenem on 30-day mortality for patients with E coli or Klebsiella pneumoniae bloodstream infection and ceftriaxone resistance: a randomized clinical trial. JAMA. 2018; 320:984-994
26. Leal HF, Azevedo J, Silva G E O. et al. Bloodstream infections caused by multidrug-resistant gram-negative bacteria: epidemiological, clinical and microbiological features. BMC Infect Dis. 2019 Jul 11; 19(1):609 doi.org/10.1186/s12879-019-4265-z
27. H. Afroz et al. A 6-year retrospective study of bloodstream Salmonella infection and antibiotic susceptibility of Salmonella enteric serovar Typhi and Paratyphi in a tertiary care hospital in Dhaka, Bangladesh. Tzu Chi Medical Journal .2014; 26: 73-78
28. Hasan M N A, Gould A P , Drennan C, Hill O, Justo J A, Kohn J , Bookstaver P B. Empirical fluoroquinolones versus broad-spectrum beta-lactams for Gram-negative bloodstream infections in the absence of antimicrobial resistance risk factors. J Glob Antimicrob Resist. 2019 Dec 27; 22:87-93.doi: 10.1016/j.jgar.2019.12.015
29. Punjabi C, Tien V, Meng L, Deresinski S, Holubar M. Oral Fluoroquinolone or Trimethoprim-Sulfamethoxazole vs ß-Lactams as Step-Down Therapy for Enterobacteriaceae Bacteremia: Systematic Review and Meta-analysis. *Open Forum Infectious Diseases*. 2019; 6(10):1-9 ofz364 https://doi.org/10.1093/ofid/ofz364
30. Banik A, Bhat S H, Kumar A, Palit A, and Snehaa K. Bloodstream infections and trends of antimicrobial sensitivity patterns at Port Blair. J Lab Physicians.2018 Jul-Sep; 10(3): 332–337
31. Vasudeva N, Nirwan P S, and Shrivastava P. Bloodstream infections and antimicrobial sensitivity patterns in a tertiary care hospital of India. Ther Adv Infect Dis. 2016 Oct; 3(5): 119–127
32. Sandhu R, Dahiya S ,Sayal P. Evaluation of multiple antibiotic resistance (MAR) index and
33. Doxycycline susceptibility of Acinetobacter species among inpatients. Indian J Microbiol Res. 2016; 3(3):299-304
34. S. Farid , A. Abouelela and M. Eliwa . Doxycycline and Co-trimethoxazole: A new combination for treatment of MDR Acinetobacter baumannii. Does it work? Int.J. Curr. Microbiol.App.Sci (2016) 5(1): 157 -164.