ORIGINAL ARTICLE

CURRENT TRENDS IN BLOOD STREAM INFECTIONS-PATHOGENS AND THEIR ANTIMICROBIAL SUSCEPTIBILITY PATTERN

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ABSTRACT

Background: Blood stream invasion by microbes is a very critical, life-threatening condition and it poses major threat to all organs of the body. Bacteremia along with systemic manifestations is septicemia which is associated with high mortality.

Objectives: To identify the bacteria responsible for blood stream infections and evaluate the antibiotic susceptibility pattern of isolated bacteria in a tertiary care hospital.

Methods: It was a Prospective Cross-sectional study conducted in the Pathology Laboratory, Sharif Medical City Hospital, Lahore from January 2019 to December 2020. The blood samples received in Microbiology laboratory, Sharif Medical City hospital, were evaluated. The blood cultures were processed for identification of pathogens and their susceptibility. Two subcultures, on day 1 and day 5 were inoculated on Blood agar and MacConkey agar. Bacterial identification was established by gram staining, bench tests, and biochemical tests. API 20E was used for Enterobacteriaceae and API 20NE for non-fermenting gram negative bacilli (NFGNB). The antimicrobial sensitivity testing of the causative bacteria was conducted, using commercially available discs, by Kirby Bauer disc diffusion assay and reported in accordance with Clinical & Laboratory Standards Institute (CLSI) 2019.

Results: Out of 754 blood cultures, 123 exhibited positive growth yielding 76(61.78%) gram negative rods, 43(34.95%) gram positive cocci while 4 (3.2%) Candida sp. Among gram positive cocci, the commonest bacterial pathogen is *Staphylococcus aureus* (51.1%), followed by *Enterococcus sp* and CONS each constituting 18.6%, and *Streptococcus sp* consisting of 11.6%. These bacteria exhibited varying resistance to all drugs being 100% susceptible to Vancomycin and Linezolid. Among Gram negative pathogens, *Pseudmonas aeruginosa* constitutes 38.2%, followed by *E. coli* (25%), *Acinetobacter* 14.5%, *Salmonella typhi* (10.5%), and others. An alarmingly poor susceptibility was observed by Gram negative bacteria (GNB) against all the drugs. Only 21.4%, 35.7%, and up to 39.7% isolates were sensitive to Ampicillin and Co-amoxiclav and third generation cephalosporins respectively. Results for carbapenem sensitivity being around 56.6%-61.8% for imipenem and meropenem respectively.

Conclusion: The study reports inadequate effectiveness of commonly used drugs which are part of empiric regimes of our clinicians. Even the broad-spectrum drugs like aminoglycosides and carbapenems which were considered last therapeutic resort previously haven't proved to possess satisfactory antimicrobial activity against majority of bacteria.

Key words: Blood stream infections, Kirby Bauer disc diffusion assay, Enterobacteriaceae

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INTRODUCTION

Blood stream invasion by microbes is a very critical, life-threatening condition and it poses major threat to all organs of the body. Bacteremia along with systemic manifestations is

septicemia which is associated with high mortality.[1] Blood stream infections (BSIs) are associated with around 20-50% annual mortality.[2] Prompt detection of such infections is a critical responsibiltiy of clinical microbiologist. Blood culture is the gold standard for isolation of causative organisms of bloodstream infections[3].The common etiological pathogens leading to septicemia include *Staphylococcus, Streptococcus, Enterococcus, Escherichia coli, Klebsiella, Salmonella, Enterobacter, Pseudomonas sp. etc.*[4,5]The dramatic surge in drug resistance has complicated successful management of infections including BSIs. Such drug resistant bugs results in prolonged hospitalization of patients, increased mortality, cost of treatment and exhaustion of resources of health care system.[6] The spectrum of causative pathogens of bloodstream infections (BSIs) vary considerably from region to region. Identification of the causative pathogens and determination of antimicrobial susceptibility of these pathogens holds a key position for optimum and prompt management of BSIs and impedes the rising antimicrobial drug resistance.[4]

Knowledge of bacterial profile, and the sensitivity and resistance patterns of causative bacteria might help to design new diagnostic approaches, treatment plans and enable policy makers to revise the guidelines for addressing antimicrobial resistance.[7] The minimum turnaround time for blood culture report is 2-3 days .The empirical antibiotic therapy is usually commenced prior to culture report in suspected cases of sepsis.[8]

Rationale: Hence, the current study was designed to identify the bacteria causing bloodstream infections in a tertiary care hospital and determine their antimicrobial susceptibility pattern. This would provide data for empirical antimicrobial therapy and create awareness in the clinicians about the rising drug resistant pathogens

OBJECTIVES

To identify the bacteria responsible for blood stream infections and evaluate the antibiotic susceptibility pattern of isolated bacteria in a tertiary care hospital.

METHODS

The study was approved by the Ethical Committee of *Sharif Medical and Dental College, Lahore,* vide No. SMDC/SMRC/103-19 Dated 28.08.2019. The Prospective cross-sectional study was carried out in the Pathology Laboratory of Sharif Medical City Hospital, Lahore. The blood samples received in Microbiology laboratory between January 2019 to December 2020, were evaluated. The study was started after getting Institutional ethical approval.

The samples for blood culture were received in blood culture bottles. These were incubated at 35°C for 5 days. First subculture was performed on blood agar and Mac Conkey agar after 24 hours. In case of no growth, the second subculture was performed on the same media on day 3 and then day 5. If no growth was isolated after the subcultures, the report of no growth was finalized after 5 days of incubation. However the positive cultures were processed for bacterial identification using colony morphology, gram staining,catalase test, coagulase test for gram positive cocci and API 20E and 20NE for gram negative rods. Direct gram staining from blood culture bottles and re culture of specimens were also carried out to rule out contamination.

The antibiotic susceptibility testing of the isolated bacteria was conducted by using the Modified Kirby Bauer disc diffusion assay. The bacterial suspension equivalent to 0.5 McFarland turbidity standard was prepared by emulsifying 3-4 colonies of bacteria in normal saline. The suspension was lawned on the Mueller-Hinton agar plates with sterile swab followed by putting antibiotic discs. These plates were incubated overnight at 35°C and the zones of inhibition were interpreted in accordance Clinical & Laboratory Standards Institute (CLSI) 2019. The antibiotics for the isolated gram positive and gram negative bacteria are as follow:

For gram negative bacteria: Ampicillin (AMP), Co-amoxiclav (AMC), Cefotaxime (CTX), Ceftriaxone (CRO), Ceftazidime (CAZ), Cefepime (FEP), Tazobactam-piperacillin (TZP), Amikacin (AK) and Ciprofloxacin (CIP), Levofloxacin (LEV), Co-trimoxazole (SXT), Imipenem (IMP), Meropenem (MEM), Doxycycline (DO) and Chloremphenicol (C) (for *S.Typhi)*. For gram positive bacteria : Penicillin (P), Ampicillin (AMP), Cefoxitin (FOX), Fusidic acid (FD), Gentamicin (CN), Doxycycline (DO), Co-trimoxaazole (SXT), Ciprofloxacin (CIP), Levofloxacin (LEV), Linezolid (LZD), and Vancomycin (VA).

On the basis of susceptibility of *Staphylococcus* to Penicillin, amoxicillin and ampicillin were reported as sensitive and resistant. On the basis of susceptibility to cefoxitin, all the β-lactam drugs and the combination of β-lactam- β lactamse inhibitor combinations were reported. *Staphylococcus aureus* resistant to cefoxitin were reported as MRSA and those isolates sensitive to Cefoxitin were reported as MSSA in accordance to CLSI guidelines.

The Statistical package for the Social Sciences 25.0 was used for data analysis.

RESULTS

Table-1 shows a total of 754 blood cultures were processed and 123 exhibited positive growths 631 were negative.

Figure1 demonstrates that among 123 organisms, 76(61.78%) were gram negative rods, 43(34.95%) were gram positive cocci while 4 (3.2%) were Candida sp.

The distribution of gram positive cocci (GPC) from blood cultures and their Susceptibility to antimicrobials is shown in Table 2. Among gram positive cocci, the commonest bacterial isolate is *Staphylococcus aureus* (51.1%), followed by *Enterococcus sp* and the probable skin contaminant (CoNS) each constituting 18.6%, and *Streptococcus sp* consisting of 11.6%.

Table 3 represents the frequency of Gram negative bacteria along with their susceptibility pattern

DISCUSSION

Blood stream infections (BSIs) caused by drug resistant bacteria is a major global challenge to mankind. This phenomenon leaves us with a handful of therapeutic options as there is a very limited arsenal of antibiotics in the pipeline.

The current study aimed at isolating the pathogens responsible for Blood stream infections and the identifying the susceptibility of these pathogens. As evident by the results, out of a total of 754 cultures, 16.3% turned out to be positive with predominance of gram-negative bacteria (61.7%) and 34.9%-gram positive cocci,3.2% candida sp. A meta-analysis and systematic review conducted on paediatric population concluded that positive blood culture was around 19.1%. Out of 4836 bacterial isolates, 2974 were Gram-negative (63.9%) and 1858 were Gram-positive (35.8%).[9]Hence, the results are concordant with the findings of our single centre study. A study by Altaf et al in SaudiArabia in 2020, also exhibited gram negative bacteria as the dominant pathogens, constituting 62.2% of blood stream infections.[4]

Table-1: Frequency of Positive Growth from Blood Culture

Blood culture	No.	%age
Positive culture	123	16.3%
Negative culture	631	83.68%
Total cultures	754	100%

Table 2: Distribution of Gram-Positive Cocci (GPC) from Blood Cultures and their Susceptibility to Antimicrobials

Antimicrobial Drugs	*Staphylococcus aureus* n=22	*Coagulae Negative Staphylococcus Species (CONS)* n=8	*Streptococcus Species* n=5	Enterococcus Species n=8	Total	%age Sensitive n=43
P	0	0	5	4	9	2.1
AMP	0	0	5	4	9	2.1
FOX	13	3	NT	NT	16	53.3
CIP	8	3	2	3	16	37.2
LEV	9	4	2	3	18	41.9
CN	7	3	NT	NT	13	37.1
DO	8	3	4	2	17	39.5
FD	14	2	3	5	24	55.8
LZD	22	8	5	8	43	100.0
VA	22	8	5	8	43	100.0
SXT	11	3	2	NT	16	45.7

NT = Not tested

Table 3: Distribution of Gram-Negative bacteria from Blood Cultures and their Susceptibility to Antimicrobials

Drug	*Salmonella Typhi*		*E. Coli*		*Klebsiella spp*		*Serratia spp*		*Pseudomonas aeruginosa*		*Acinetobacter spp*		Total	%age Sensitive
	n=8 (10.5%)	%	n=19 (25%)	%	n=6 (7.9%)	%	n=3 (3.9%)	%	n=29 (38.2%)	%	n=11 (14.5%)	%		
AMP	0	0	5	26.3	1	16.7	0	0	-	-	-	-	6	21.4
AMC	NT	NT	9	47.4	1	16.7	0	0	-	-	-	-	10	35.7
CTX	NT	NT	7	36.8	1	16.7	0	0	-	-	2	18.2	10	25.6
CRO	3	37.5	7	36.8	1	16.7	0	0	-	-	2	18.2	13	27.7
CXM	3	37.5	-	-	-	-	-	-	NT	NT	NT	NT	3	37.5
CAZ	-	-	6	31.6	0	0.0	0	0	18	62.1	3	27.3	27	39.7
FEP	-	-	8	42.1	2	33.3	0	0	20	69.0	4	36.4	34	50.0
SAM	-	-	9	47.4	3	50.0	0	0	NT	NT	8	72.7	20	51.3
DO	-	-	4	21.1	0	0.0	0	0	NT	NT	9	81.8	13	33.3
TZP	-	-	9	47.4	3	50.0	1	33.3	11	37.9	7	63.6	31	45.6
AK	-	-	11	57.9	4	66.7	1	33.3	12	41.4	4	36.4	32	47.1
CIP	4	50	6	31.6	1	16.7	0	0	10	34.5	1	9.1	22	28.9
C	0	0	-	-	-	-	-	-	-	-	-	-	0	0.0
SXT	0	0	3	15.8	1	16.7	0	0	-	-	2	18.2	6	12.8
IPM	8	100	12	63.2	2	33.3	2	66.7	15	51.7	4	36.4	43	56.6
MEM	8	100	13	68.4	3	50.0	2	66.7	17	58.6	4	36.4	47	61.8
ATM	-	-	-	-	-	-	-	-	7	24.1	-	-	7	24.1
AZM	8	100	-	-	-	-	-	-	-	-	-	-	8	100

Among gram positive cocci, the commonest bacterial species identified in the current study is *Staphylococcus aureus* (51.1%) of gram positive cocci, followed by *Enterococcus sp* and the skin colonizer,CoNS each constituting 18.6%, and *Streptococcus sp* consisting of 11.6% .The results are in contrast to a study by Maharath and his colleagues in 2021, which concluded CONS to be the most frequent pathogen in BSIs accounting for 50.9% in BSIs among male population.[10] Another research conducted on device associated infections, reported skin contaminants such as CoNS, *S.aureus, and candida sp* to be the major organisms responsible for most of the central line-associated bloodstream infections.[11] The findings of our study are in agreement to a six year retrospective study revealing *Staphylococci* as the commonest pathogen (65.5%), followed by *Enterococcus spp* (17.5%), *Streptococcus spp* (7.1%). [12]

The current study concluded that Gram negative bacteria (GNB) constitute the major bulk of BSIs and among gram negative bacteria, NFGNB (non fermenting gram negative bacteria) are emerging pathogens as 52.6% of gram negative bacteria consisted of NFGNB. Our results don't agree to an Indian study revealing only 32.68% gram negative bacilli (GNB) in BSI. However, out of GNB isolated, the study showed that 30.1% were NFGNB.[13] The commonest pathogen in the current study turned out to be *Pseudomonas aeruginosa* (23.5%), followed by *Staphylococcus aureus* (17.88%), *E.coli* (15.44%), and *Acinetobacter sp* (8.9%), and *S.*Typhi (6.5%). The results are dissimilar from a surveillance program documenting *Staphylococcus aureus* as the major pathogen (20.7%), followed by *Escherichia coli* (20.5%), *Klebsiella pneumoniae* (7.7%), *Pseudomonas aeruginosa* (5.3%), and *Enterococcus faecalis* (5.2%).[14]

As for as antimicrobial susceptibility of gram positive bacteria is concerned, it is observed in the current study that 59.1% isolates of *Staphylococcus aureus* are MSSA (Methicillin sensitive *Staphylococcus aureus*) and 41.9 % isolates are MRSA (Methicillin resistant *Staphylococcus aureus).*The results are concordant to the results of the study by of Rodrigo et al that showed a range of MRSA from 41.9% to 47.3% from year 2010-2016.[15] The fluoroquinolones tested in the above study i-e ciprofloxacin and levofloxacin exhibited around 37.2% and 41.9% susceptibilty to Gram positive cocci. The results are contrary to a systematic review conducted in Ethopia, reporting only 7.4 to 18.6% resistance to fluoroquinolones in GPC[16]. The difference in the findings might be because of injudicious use of this group of drug in our region as the drug is the usual component of empirical regimes. Melkam Birru and his colleagues,2021 documented 66.7% susceptibility to gentamicin (excluding enterococci), 23.1 % to penicillins and 38.5% to doxycycline respectively in GPC.[17] However, our study isolates exhibit much higher resistance being only 2.1 % susceptible to penicillin, 37.1% to gentamicin and 39.5% to doxycycline. In current study all isolated gram-positive cocci were 100% sensitive to Vancomycin and linezolid. Hence, proving these drugs to be still therapeutic options for multidrug resistant pathogens.

The gram-negative bacteria isolated in our study didn't show satisfactory susceptibility to the conventional drugs. Only 21.4%and 35.7% isolates were susceptible to Ampicillin and Co-amoxiclav. As for as susceptibitity to cephalosporins is concerned, a susceptibility range of 27.5-39.7%was observed for third generation cephalosporins. Only cefipime (fourth generation cephalosporins was active against 50% isolates, *Pseudomonas aeruginosa* being 69% sensitive. Our findings don't correspond to a German study reporting only upto 14.9% resistance to third generation cephalosporins.[18]The β-lactam – βlactamase combinations were also assessed for their efficacy and 51.3 and 45.6% isolates were susceptible to Sulbactam-Ampicillin,and Tazobactam piperacillin respectively. Other drugs also exhibit poor activity against Gram negative bacteria with only co-trimoxazole (12.8%), ciprofloxacin (28.9%) and Amikacin (47.1%). Among S. Typhi isolates,100% were MDR and 50% were XDR. Another study in Lahore reported 32% MDR and 40% XDR Typhi.[19] While Similar high resistance among GNB findings has been reported in other studies.[18] Such high resistance may be attributed to factors like unsupervised drug dispensing practices in the community and injudicious use of antibiotics in our hospitals. Among carbapenems, Imepenem and meropenem were tested, 100%isolates of *Salmonella* Typhi exhibited susceptibility to these drugs, and none of the isolate exhibited resistance to Azithromycin. Though another study conducted in Lahore by Kokab et al reported 6.6% S.Typhi isolates resistant to Azithromycin as determined by disc diffusion technique.[20]As far as other members of enterobacteriaceae are concerned, 63-68% *E.coli and Serratia* species in the current study were susceptible to the tested carbapenems. *Klebsiella sp* showed 33.3% susceptibility to imepenem and 50% to meropenem. Among NFGNB, 51.7% and 58.6% *Pseudomonas aeruginosa* were susceptible to Imepenem and meropenem respectively. But carbapenems didn't prove to be much effective against *Acinetobacter sp* exhibiting only 36.4% susceptibility to this group. Contrary to our findings much better susceptibility was observed in an Indian study reporting >66.6% susceptibility to Amikacin and >88.8% susceptibility to carbapenems[21]

CONCLUSION

The study reports inadequate effectiveness of commonly used drugs which are part of empiric regimes of our clinicians. Even the broad-spectrum drugs like aminoglycosides and carbapenems which were considered last therapeutic resort previously haven't proved to possess satisfactory antimicrobial activity against majority of bacteria causing BSIs. This alarming rise in antimicrobial drug calls for judicious use of antibiotics.

LIMITATIONS

It is a single centre study, so large scale studies need to be conducted in future with a larger population size inducting and patients from various hospitals.

RECOMMENDATIONS

Keeping in mind the high resistance among bacteria, following recommendations are made:

- Blood culture and sensitivity is mandatory in all clinically suspected cases of BSIs to prevent the critical issue of emerging drug resistance
- Though upcoming drugs are limited, still combination drugs such as Ceftazidime-avibactam, Meropenem-vaborbactam should be evaluated for such resilient pathogens. This might help to revise the empiric therapy for life threatening BSIs and prevent the treatment failures.

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AUTHOR'S CONTRIBUTIONS

SI: Conceived, planning, manuscript writing, data collection
SI: Discussion, help in references
IYK: Proof reading, help in references
KJ, MTS: Critical revision, Proof reading
SH: Proof reading, data collection