

Original Research Article

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Secular Trend of Antibiotic Resistance in Blood Stream Infections-A retrospective Analysis

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ABSTRACT

Bloodstream infections (BSIs) are among the most serious infections acquired by hospitalized patients requiring intensive care. The existence of a pathogen population with an ever-increasing resistance to antibiotics has complicated the clinical problems. This retrospective study was undertaken with a view to compile and analyse the common isolates of BSIs along with resistance pattern in a tertiary care teaching hospital. Retrospective study was conducted to identify the microbial profile in the blood culture isolates and their antibiotic susceptibility patterns in a tertiary care teaching hospital. The reports of specimens submitted for blood culture during the period of 2012-2015 to the microbiology laboratory were obtained, the positive cultures were identified, and data on the microbial species and their antibiotic patterns were collected and statically analysed. There were 4964 blood culture samples, of which 543 were identified to be culture positive. Of the total culture positives 177 (32.59%) were Gram positive bacteria; 309 (56.91%) were gram negative bacteria and 57 (10.50%) were *Candida species*. Among the gram positive bacteria 150 (27.62%) were Coagulase negative Staphylococci (CoNS); 16 (2.94%) were *Staphylococcus aureus* and 11 (2.02%) were Enterococcus species. In the Gram negative bacteria *E.coli* was 140 (25.78%); *Klebsiella pneumonia* was 92 (16.94%); *Acinetobacter* species was 25 (4.60%); *Pseudomonas species* was 32 (5.89%). Statically significant resistance was observed in CoNS for Oxacillin; in *E.coli* for Ciproflaxacin, Amoxicillin-clavulanic acid, Piperacillin + tazobactam, Cefuroxime; and in *Klebsiella pneumoniae* for Amoxicillin-clavulanic acid, Piperacillin+tazobactam, Imipenem. CoNS is the common gram positive isolates followed by *E.coli* and *Klebsiella pneumoniae* in gram negative organisms of BSI in our setup. Significant resistance was observed for third generation cephalosporins, fluoroquinolones and piperacillin +tazobactam combination. Ongoing surveillance for antimicrobial susceptibility remains essential in case of BSI and will enhance efforts to identify resistance and attempt to prevent its spread.

Keywords

Blood Stream
Infections (BSIs),
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Introduction

One of the major global problems is the rising trend in antibiotic-resistance mainly in hospitals, and also in the community which

is a difficult condition to control without considerable measures and resources. The consequences of increased drug resistance are by far-reaching beyond any doubt when

it is concerned with Blood stream Infection (BSI) making antibiotic resistance an important health issue. In many countries antimicrobial resistance among bloodstream pathogens have severe consequences including increased health care cost, morbidity and mortality. This is especially true in countries like India, where, antibiotics are used extensively and considerable resistance is reported from all over the country.

BSI is potentially life-threatening condition and requires rapid identification with the antibiotic susceptibility pattern of the causative agent in order to facilitate specific antimicrobial therapy. Despite the availability of newer antibiotics, emerging antimicrobial resistance has become an increasing problem in many pathogens throughout the world. The organisms responsible for bacteraemia vary across geographical boundaries; but few of the pathogens like *E. coli*, *Klebsiella spp.*, *Staphylococcus aureus*, *Coagulase negative Staphylococci (CoNS)*, *Pseudomonas spp.*, *Salmonella spp.* and *Acinetobacter spp.* are constantly associated with bacteraemia because of their frequent isolation and multi-drug resistance which has reached worrying levels. Also some phenotypes such as MRSA, VRE, MR-CoNS, and Carbapenamase producing gram negative organisms such as *P.aeruginosa* & *Acinetobacter baumannii* are of particular concern. Even central venous catheter, invasive devices, surgery and long term stay in ICUs puts the patients at higher risk of BSI.

For practicing physicians, clinical microbiologists and public health officials, knowledge of local antimicrobial resistance patterns is essential to guide empirical and pathogen specific therapy. This information is also critical for optimal decisions regarding formulation of hospital infection

control policies, rational public healthcare policies, and national and international research agendas in that area. Antimicrobial resistance surveillance is essential to track changes in microbial populations, estimate the magnitude of the problem and to design and evaluate interventions. However, there is no national level information on resistance among bacteria causing bloodstream infections in India.

Therefore, the present study was a modest attempt with an objective to evaluate the bacteriological profile and tracing resistance among patients with BSI at our hospital. This study also summarizes the strategic resistance patterns of the isolated organisms from the patients admitted in our tertiary care hospital.

Materials and Methods

This retrospective analysis on blood culture-positive isolates and their antimicrobial susceptibility pattern was carried out during the period starting from 2012-2015 in a tertiary care teaching hospital in southern Rajasthan. Approval for the study was obtained from hospital ethics committee and consent was waived since this is a retrospective evaluation. Only one blood isolate per patient was included in the study. The blood sample were collected in BacT/ALERT FA (adult) and BacT/ALERT PFplus (paediatric) bottles; and received in the department. Inoculated bottles were incubated in BacT/ALERT 3D (Biomérieux) and growth indicated bottles were processed as per company instructions. Identification of microorganisms to species level and antimicrobial susceptibility testing was performed with the automated system vitek 2 compact (Biomérieux).

Statistical analysis was conducted using Microsoft excel 2010. Chi-square test was applied for the comparison of categorical

variables. *p* values less than 0.05 were considered as statically significant.

Results and Discussion

A total of 543 isolates from 4964 blood specimens cultured were analysed during study duration of 2.5 years (2012-2015). The overall culture positivity rate thus obtained was 10.93%. Out of the total isolates analysed, 84.71% were from intensive care units and rest 15.28% were from different wards (Table no.I).

The relative distribution frequency of blood isolates is depicted in table no. II. The aerobic or facultative bacterial isolates was found to be 89.50% and candida species were 10.50%. Among the pathogens; the most common isolates were 27.62% Coagulase negative staphylococci (CoNS), 25.78% *Escherichia coli*, 16.94% *Klebsiella pneumoniae*, 5.89% *Pseudomonas aeruginosa* and 5.70% *Non-albicans Candida species*.

The resistance pattern to antibiotics for gram negative isolates and gram positive isolates is shown in table no. III and IV respectively.

According to global surveillance reports, bloodstream isolates are the best candidates for the study of antimicrobial susceptibility of human bacterial pathogens. Patients with bacteraemia have remained a treatment challenge. The present study illustrates the BSI bacterial spectrum and antimicrobial resistance pattern in a tertiary care teaching hospital of southern Rajasthan.

During the study period a total 4964 blood samples for aerobic bacterial culture were received in the department for processing, of which 543 were culture positive; with an over all culture positivity rate of 10.93%. Similar rate of blood culture

positivity of 12.7% was also reported by Chand wattal *et al.*,, from north India. Several studies across India have reported a varied range of positivity ranging from 3.72% to 44%.The varying rates of blood culture depends upon numerous factors such as the number and amount of blood cultures taken, the system and type of blood culture medium used for bacterial detection. In addition to this most of the patients already received some kind of antibiotics before they come to the tertiary care hospital and self-medication is very common because of the counter availability of medicines (Asmita Ashok, 2016).

In the present study, Gram negative bacteria was found to be responsible for 56.90% and Gram positive bacteria caused 32.59% of the BSI. This observation is similar to the various studies done in the patients of developing countries (Vanitha 21-24). In the study conducted by Vanitha *et al.*, had reported 59.1% of gram negative organisms and 37.7% gram positive organisms. Similarly Mehta *et al.*,, also have reported gram negative organisms as the primary cause of BSI but with a higher rate of 80.96%; whereas only 18% were gram positives organisms in their study.

In the present study, CoNS were the most commonly isolated Gram positive cocci with an isolation rate of 27.62%, followed by the isolates of *S. aureus* and *Enterococci* contributing only 2.94% and 2.02% of respective isolation rates. In contrast, Asmita Patil *et al.*, and Rakhee baby *et al.*, have reported a higher isolation rate of 27.66% and 21.46% for *S. aureus*. Similar to our CoNS isolation rates; Chand Wattal also have reported 20.3% in blood. Anu Gupta *et al.*, and Mukherjee *et al.*, also had reported CoNS as most common Gram positive isolate; but with different isolation rates of 9.1% and 61% individually. Similar studies

from other countries carried out by Karlowsky *et al.*, and Japoni *et al.*, had reported 42% and 67.7% CoNS respectively. Previously, CoNS isolated from blood culture were considered as contaminants. But in recent years because of the increased use of intra-vascular devices, increase in immunocompromised patients and propensity to form biofilm by the organism; they are now considered as important agent for nosocomial bacteraemia. Meticulous skin disinfection at the time of venepuncture, determination of time to positivity, clinical correlation and appropriate antimicrobial therapy to prevent cross transmission from patient-to-patient can help to differentiate CoNS as potential contaminants or as true pathogens (Cockerill *et al.*, 1997, Kumar Y *et al.*, 2001). Also interpretation of blood cultures that are positive for CoNS require careful reasoning (Anu Gupta, 2010).

Among the Gram negative isolates, *E.coli*, (25.78%) was the primary isolate followed by *Klebsiella pneumoniae* (16.94%), *P.aeruginosa* (5.89%), and *Acinetobacter ssp.* (4.60%). Similarly *E.coli* were reported to be most common gram negative bacilli from BSI in many studies. (Vinitha). Kalpesh Gohel *et al.*;; Wagner *et al.*, also reported *E.coli* as commonest gram negative isolate in BSI. Although Kumar *et al.*, reported predominance of *Klebsiella* bacteraemia; in the current analysis it was the second most common gram negative organism. This diversity in the frequency can be justified due to the difference in the study plan, geographical location, seasonal variation, hospital infection control policies and disparity of the etiological agents (Asmita Ashok Patil, 2016).

In the present study, *Candida* spp. accounted for 10.50% of the BSI pathogens (5.70% Non-albicans candida and 4.78% *Candida*

albicans). This data is comparable to the studies conducted by Anu Gupta *et al.*, (13%) and Chand Wattal *et al.*, (17.5%). According to surveillance data from the US centre for disease control and prevention, candida accounts for 12% of all hospital acquired BSIs (Hidron *et al.*, 2008). The fungal BSI are on rise due to extensive use of antibiotics, aggressive treatment of various diseases, increasing use of invasive devices, an increasing surviving AIDS patients etc. (Anu Gupta, 2010). These all factors in addition to solid organ malignancy, previous surgery, and increase in use of antifungal agents also contributed for the same (Chand Wattal, 2014).

The antimicrobial resistance pattern in the present study for Gram positive isolates was statically significant only for Oxacillin in CoNS isolates during the study period .Anu Gupta *et al.*, also had stated increased methicillin resistant during the two year study periods. This indicates that infections by CoNS may constitute a significant threat to septicemia in our locale and the spectrum of organisms is subject to geographical alterations. We report 100% sensitivity to vancomycin and linezolid in *Staphylococcus aureus*; whereas vancomycin resistance of 36.36% (4/11) in Enterococci was noted with 100% linezolid sensitivity. Anu Gupta *et al.*, also had reported 16.8% vancomycin resistance in Enterococci. The possible explanation for this may be due to lower number of isolates of *S. aureus* in comparison to CoNS; and may be the judicious use of vancomycin and linezolid in our setup.

Among the Enterobacteriaceae; *E. Coli* and *Klebsiella pneumonia* were the commonest to be isolated. Stastical comparison was done between the resistance pattern of isolated strains in the year 2012-2013 and 2014-2015. Statistically significant

resistance was observed for Ciprofloxacin, Amoxicillin-clavulanic acid, Piperacillin-tazobactam, and Cefuroxime in *E.coli*. Imipenem did not show any significant resistance in *E.coli* during study period. In *Klebsiella pneumoniae* Amoxicillin-clavulanic acid, Piperacillin-tazobactam, and Imipenem were significantly resistant. Anu Gupta *et al.*, also had reported alarming increase of resistance for most of the

antibiotics during the study period. Also there was increase in the imipenem resistance in *E.coli*.

Among the Non-Enterobacteriaceae; no significant resistance was observed for any antibiotics during the study period. The possible explanation may be the fewer isolates of *Pseudomonas* species and *Acinetobacter* species.

Table.1 Distribution of positive blood cultures based on location of the patient (ICU & Wards)

Location	2012	2013	2014	2015	Total
ICUs	73	101	133	153	460 (84.71%)
Wards	17	21	28	17	83(15.28%)

Table.2 Year wise distribution of number of blood isolates

Micro-organism	2012 (n=90)	2013 (n=122)	2014 (n=161)	2015 (n=170)	Total (n=543)
Gram positive bacteria					
CONS	26	32	41	51	150 (27.62%)
Staphylococcus aureus	00	04	07	5	16 (2.94%)
Enterococcus species	03	02	02	4	11 (2.02%)
Total gram positive	29	38	50	60	177 (32.59%)
Gram negative bacteria					
Escherichia coli	30	34	40	36	140 (25.78%)
Klebsiella pneumoniae	10	21	28	33	92 (16.94%)
Acinetobacterbaumani	02	05	09	09	25 (4.60%)
Pseudomonas aeruginosa	04	07	09	12	32 (5.89%)
Others	03	04	07	06	20 (3.68%)
Total gram negative	49	71	93	96	309 (56.91%)
Candida albicans	06	06	08	06	26 (4.78%)
Candida ssp. (Non albicans)	06	07	10	08	31 (5.70%)
Total fungi	12	13	18	14	57 (10.50%)

Table.3 Trend of antimicrobial resistance in Gram positive bacteria

Organism/ Antibiotic	2012	2013	2014	2015	2012- 2013	2014- 2015	P value	
CONS								
Oxacillin	12/26	31/32	45/41	47/51	43/58	92/92	<0.0001	Statistically significant
Gentamicin	4/26	6/32	08/41	08/51	10/58	16/92	1	Not significant
Vancomycin	0/26	0/32	1/41	0/65	00/58	01/92	0.444	Not significant
Linezolid	0/26	0/32	1/41	1/65	00/58	02/92	0.278	Not significant
Staphylococcus aureus								
Oxacillin	00/00	2/4	4/7	3/5	02/04	07/12	0.780	Not significant
Gentamicin	00/00	1/4	1/7	0/5	01/04	01/12	0.369	Not significant
Vancomycin	00/00	00/04	00/07	00/05	00/04	00/12	NA	
Linezolid	00/00	00/04	00/07	00/05	00/04	00/12	NA	
Enterococcus								
Vancomycin	00/03	01/02	01/02	02/04	01/05	03/06	0.303	Not significant
Linezolid	00/03	00/02	00/02	00/04	00/05	00/06	NA	

Table.4 Trend of antimicrobial resistance of blood isolates in gram negative bacteria

Organism/antibiotic	2012	2013	2014	2015	2012- 2013	2014- 2015	p- value	
E. coli								
Amikacin	06/30	5/34	4/40	7/36	11/64	11/76	0.623	Not significant
Ciproflaxacin	20/30	28/34	36/40	33/36	48/64	69/76	0.018	Statistically significant
Amoxi-clav	04/30	6/34	14/40	17/36	10/64	31/76	0.001	Statistically significant
Piperacillin+Tazobactam	02/30	05/34	08/40	12/36	07/64	20/76	0.015	Statistically significant
Cefuroxime	02/30	4/34	08/40	09/36	06/64	17/76	0.036	Statistically significant
Imipenem	0/30	0/34	1/40	1/36	00/64	02/76	0.255	Not significant
Klebsiella								
Amikacin	4/10	08/21	11/28	11/33	12/31	22/61	0.850	Not significant
Ciproflaxacin	08/10	17/21	21/28	26/33	25/31	47/61	0.742	Not significant
Amoxi-clav	2/10	4/21	11/28	16/33	06/31	27/61	0.017	Statistically significant
Piperacillin+Tazobactam	2/10	4/21	14/28	19/33	06/31	33/61	0.001	Statistically significant
Cefuroxime	1/10	2/21	4/28	6/33	03/31	10/61	0.355	Not significant
Imipenem	0/10	1/21	8/28	11/33	01/31	19/61	0.002	Statistically significant
Acinetobacter								
Amikacin	1/2	3/5	4/9	5/9	04/07	9/18	0.753	Not significant
Gentamicin	1/2	1/5	1/9	1/9	02/07	02/18	0.294	Not significant
Ciproflaxacin	1/2	3/5	6/9	6/9	04/07	12/18	0.674	Not significant
Imipenem	1/2	1/5	3/9	4/9	02/07	07/18	0.638	Not significant
Piperacillin+Tazobactam	1/2	2/5	4/9	5/9	03/07	09/18	0.719	Not significant
Pseudomonas								
Amikacin	2/4	2/7	1/9	2/12	04/11	03/21	0.150	Not significant
Ceftazidime	2/4	3/7	2/9	2/12	05/11	04/21	0.119	Not significant
Ciproflaxacin	2/4	1/7	3/9	3/12	03/11	06/21	0.952	Not significant
Piperacillin+Tazobactam	0/5	1/7	1/9	2/12	01/11	03/21	0.682	Not significant
Imipenem	1/5	2/7	2/9	3/12	03/11	05/21	0.802	Not significant

One of the important outcomes of the present study was the relief for intensivists

that resistant level of life saving drugs like Meropenem and Imipenem has not yet

increased to alarming stage. Thus these antimicrobials can be used as an early commencement treatment and later deescalate which can play a vital role in reducing morbidity and mortality in BSI. The basis for this early treatment is the information about the likely pathogen and its antibiotic resistance pattern. Present study provides much needed information on the prevalence and antibiotic sensitivity pattern of prevalent blood pathogens. The analysis of resistance will help in formulating antibiotic policy and to decide the vacation period for any antibiotic in particular if required. The data will also help in limiting the indiscriminate use of antibiotics (Asmita *et al.*, 2016). The main forces driving the increase in antimicrobial resistant bacteria are poor infection control practices and inappropriate use of antibiotics. Specific antibiotic utilization strategies like antibiotic restriction, combination therapy, and antibiotic recycling may help to decrease or prevent the emergence of resistance. Specific usage based on susceptibility testing may also reduce the incidence of BSIs (Vanitha).

In the current study, we also acknowledge several limitations to our study. First this is a single centre study and may not reflect the true status of the antimicrobial pattern. Second, the duration of the study is short and needed to be extended to get a prolific result. Though the fungaemia was seen due to *Candida* isolates (non-albicans), data from antifungal susceptibility could be added benefit.

In conclusion, the present study revealed that Gram negative bacilli i.e. *E. coli* and *Klebsiella pneumoniae* predominantly an leading cause of BSI in our tertiary care setup; followed by CoNS. The significance of CoNS bacteraemia should be evaluated better in light of clinical profile of patient. In

present study, increased resistance was observed in CoNS for oxacillin; an alarming increase of antibiotic resistance for various antibiotics was noted for *Klebsiella pneumoniae* during study period. *E.coli* showed significant resistant to Ciprofloxacin, Amoxicillin-clavulanic acid, Piperacillin- tazobactam, and Cefuroxime in *E.coli* with no increase in carbapenems resistance. This calls for implementation of strict antibiotic prescribing policies and hospital infection control guidelines. Ongoing surveillance for antimicrobial susceptibility remains essential in case of BSI and will enhance efforts to identify resistance and attempt to prevent its spread.

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