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ETIOLOGICAL LANDSCAPE OF MICROORGANISMS CAUSING BLOOD STREAM INFECTIONS: COMMENSAL? OR PATHOGEN?

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ABSTRACT

Background: Blood Stream Infections (BSI's) are becoming the cause of increased hospital stay, health-care costs and high mortality rate among hospitalized patients. **Aim:** The present study was conducted with the aim of understanding the epidemiology of BSI and to raise the questions regarding the identification and reporting of pathogens and commensals/contaminants in culture positive blood samples. **Materials & Methods:** The present prospective study was conducted in the department of Microbiology of a teaching tertiary care hospital. A total of 1865 blood samples were processed through automated culture method. The samples that flagged culture positive were further processed through automated identification method. **Results & Discussion:** A total of 499 (26.7%) samples were found to be culture positive among which 51.8% isolates were Gram Positive bacteria, 42.3% were Gram Negative Bacteria and 5.7% were fungal (yeast) isolates. The isolates included several skin commensals and few rare/unusual emerging blood borne pathogens apart from the usual pathogens. After considering each isolate as a pathogen, it was identified up to the species level and reported to clinicians along with the note highlighting the basic and clinical features of the particular isolate. Useful lessons learned after analyzing the etiology of BSI helps the clinicians to understand the severe illnesses and the causative agents constantly associated with the disease. **Conclusions:** It is essential for the microbiologist to make the clinicians aware about the originality and severity of an organism so that he/she can corelate the reports clinically and proceed for the empirical therapy in the absence of sensitivity reports.

KEYWORDS: Blood stream infection, automated blood culture, Vitek-2 Compact.

INTRODUCTION

Blood Stream Infections (BSI) are known to be the major cause of morbidity and mortality in hospitalized patients. Apart from high mortality rates, they are also responsible for prolonged hospital stay and increased health care costs. Furthermore, inadequate empirical therapy of such infections is associated with adverse outcomes.[1,2,3,4]

BSI's are common in the extremely vulnerable populations of the hospital that are at the increased risk of getting infected through multiple invasive therapeutic and diagnostic procedures.[1] BSI's have been a global concern and its proper management remains as a constant challenge for health care workers.[4,5] Rapid and accurate diagnosis of BSI is crucial for the survival of infected patients.[6] Bacterial and fungal pathogens are known to be the important cause of BSI. Identification of these pathogens in the patient's blood is of immense diagnostic and prognostic importance.[2] The epidemiology of BSI is continuously changing over time and is known to be affected by geographical location, age, co-morbid illnesses and its level of economic development.[4,5,7] The impact of specific etiologic agents on BSI patient outcome is tremendous.[2]

Data regarding the epidemiology of BSI are crucial for enabling the clinicians to direct antimicrobial therapy appropriately and for the designing of preventive measures.[7]

The present prospective study has been designed to study the etiology of BSI among hospitalized patients of a teaching tertiary care hospital over a period of one year. The present study has tried to raise the questions regarding the identification of pathogens and commensal organisms in the culture positive blood samples as well as on the importance of correct reporting procedures.

METHODOLOGY

The present prospective observational study was conducted in the department of Microbiology of a teaching tertiary care hospital located in central India from January 2016 to December 2016. It was approved by the institutional ethical committee. At least one set of venous blood per patient from admitted patients of non-super specialty as well as super-specialty patient population was drawn for culture. No discrimination was made on the basis of age and gender. Five to ten ml. of blood samples were aseptically collected in commercially sourced pediatric and adult aerobic automated blood culture bottles before the administration of antibiotics. They were processed using automated BacT/Alert microbial

detection system (Becton Dickenson Microbiology system, NJ, USA). Sampling and transport were done according to the standard procedures. All blood culture bottles that flagged positive were evaluated initially by examining Gram stained smear of the broth. The culture positive samples were simultaneously inoculated on Blood agar and Mac Conkey agar media and were incubated at 37^{o}C for 16-18 hours, which was extended for up to 48 hours in case of fungal isolates. The sample was also inoculated on chocolate agar and incubated at 36^{o}C for 24~48 hours in presence of 5% CO_2. Both the standard conventional & automated (Vitek-2 compact, Biomeriux, France) methods were used to identify the microbial isolates. Bottles were incubated in the BacT/Alert machine for 7 days before reporting the sample as sterile. The negative bottles were subjected to Gram staining and sub-culture prior to discarding them.[2,7,8,9,10,11]

RESULTS AND DISCUSSION

A total of 1865 blood samples were collected from hospitalized patients revealing the clinical signs of Systemic Inflammatory Response Syndrome (SIRS) and/or sepsis. Among these, 499 (26.7%) samples were found to be culture positive from which 501 microbial isolates were obtained (two samples had two pathogens each). Among these, 260 (51.8%) isolates were Gram Positive bacteria, 212 (42.3%) were Gram Negative bacteria and 29 (5.7%) were Gram Positive Yeasts. The complete list of organisms isolated from all the positive blood samples have been listed in tables 1, 2 and 3. Among the various Coagulase Negative Staphylococcus (CoNS), the species identified were *S.hemolyticus, S.hominis, S.epidermidis, S. warneri, S. arlettae, S.sciuri, S.capitis* and *S.equinus.*

Table. 1: List of Gram Positive bacterial isolates obtained from culture positive blood samples.

S. No	Group of Gram Positive Bacterial isolate	Name of the bacterial isolate	Number of isolates(260)	Percentage of isolates (51.8%)
1	Gram Positive Cocci	*Staphylococcus aureus*	37	14.2
2		CoNS	195	75
3		*Streptococcus pyogens*	01	0.38
4		*Enterococcus faecium*	09	3.4
5		*Enterococcus fecalis*	04	1.5
6		*Kokuria kristinae*	03	1.1
7		*Kokuria rosea*	02	0.7
8		*Leuconostoc mesenteroides*	02	0.7
9		*Micrococcus luteus*	04	1.5
10		*Aelococcus otitis*	01	0.38
11		*Aerococcus viridans*	01	0.38
12	Gram Positive Bacilli	Diphtheroids	01	0.38

Table. 2: List of Gram Negative bacterial isolates obtained from culture positive blood samples.

S. No	Group of Gram Negative Bacterial isolate	Name of the bacterial isolate	Number of isolates(212)	Percentage of isolates (42.3%)
1	Members of Enterobacteriaceae	*Escherichia coli*	29	13.6
2		*Klebsiella pneumonia*	75	35.3
3		*Proteus mirabilis*	01	0.4
4		*Enterobacter cloacae* complex	01	0.4
5		*Enterobacter cloacae dissolvens*	12	5.6
6		*Enterobacter aerogenes*	02	0.9
7		*Pantoea agglomerans*	03	1.4
8		*Serratia marcescens*	03	1.4
9		*Salmonella typhi*	08	3.7
10		*Salmonella enterica*	01	0.4
		Salmonella paratyphi	04	1.8
11		*Yersinia enterocolitica*	01	0.4
12	Members of Non-Fermenter	*Pseudomonas aeruginosa*	18	8.4
		Pseudomonas stutzeri	04	1.8
		Burkholderia cepacia	15	07
		Sphingomonas paucimobilis	02	0.9
		Stenotrophomonas maltophila	01	0.4
		Acinetobacter Baumanni complex	05	2.3
		Acinetobacter baumanni	12	5.6
		Acinetobacter lwoffi	03	1.4
		Aeromonas caviae	02	0.9
		Ralstonia mannitoliilytica	02	0.9
		Achromobacter xylooxidans	01	0.4
		Achromobacter denitrificans	02	0.9
		Roseomonas gilderi	01	0.4
		Comamonas testosteroni	01	0.4
		Methylobacterium	01	0.4
		Brucella melitensis	01	0.4
		Cronobacter dubiliensis	01	0.4

Table. 3: List of Gram Positive Yeast isolates obtained from culture positive blood samples.

S. No	Group of Gram Positive Yeast isolate	Name of the Yeast isolate	Number of isolates(29)	Percentage of isolates (5.7%)
1	GramPositive Yeast likefungi	*Candida albicans*	12	41.3
2		*Candida glabrata*	09	31
3		*Candida krusei*	06	20.6
4		*Candida tropicalis*	01	3.4
5	Gram Positive true yeast	*Cryptococcus neoformans*	01	3.4

In the present prospective study, 499 (26.7%) samples were found to be culture positive indicating the prevalence of BSI as 26.7%. This is much more than that detected in the studies conducted by other authors in different geographical locations.[1,5] This is because most of them have excluded CoNS from their list of pathogens considering it to be a skin commensal and a normal contaminant of blood samples. If we would have excluded 195 CoNS from our positive cases then the prevalence of BSI comes out to be 16.3%. If we again excluded other Gram Positive organisms (except *S.aureus*, *Streptococcus* spp and *Enterococcus* spp) detected in our positive samples then the prevalence of BSI in our study would have been 15.6%. However, CoNS has been considered as a nosocomial pathogen among immuno compromised population.[8] If we also exclude the rare Gram Negative isolates (*except Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Salmonella typhi, Burkholderia cepacia* and *Acinetobacter baumanni*) from our list then our BSI prevalence rate comes out to be 14.4%.

The estimated prevalence of BSI i.e 14.4% in our case after excluding all the rare Gram Negative isolates (assuming them as contaminants) is almost equivalent to those detected by authors in their respective studies.[1,4] However, we haven't excluded any of the isolates from our list and have assumed each and every isolate as a pathogen. Among the total 501 isolates detected in our study, 260 (51.8%) were Gram Positive bacteria, 212 (42.3%) were Gram Negative bacteria and 29 (5.7%) were yeasts. Comparatively, higher percentage of Gram Positive isolates were detected in our study which was similar to those detected in other studies.[1,2,3] Our study detected 29 (5.7%) fungal isolates which was almost similar to those detected by other authors.[5,8]

CoNS (38.9%) was the most frequently isolated organism in our study as also seen in other studies[1,5,8] followed by members of Enterobacteriaceae (27.9%) followed by members of non-fermenter (14.3%). CoNS (75%) were the predominant Gram Positive isolate followed by *S.aureus* (14.2%). *Klebsiella pneumoniae* (53.5%) was the member of Enterobacteriaceae detected in highest number followed by *Escherichia coli* (20.7%). This was similar to the results obtained in one of the related studies.[7] *Pseudomonas aeruginosa* (25%) was the maximum number of non fermenter followed by *Acinetobacter baumanni* (23.6%). It has been observed that different studies conducted at different geographical locations detected different isolates that were predominantly responsible for BSI among hospitalized patients.

Some studies detected *Salmonella typhi* as the most common blood borne pathogen[4], others detected *Streptococcus* spp[2] *and S.aureus*[7] as the predominant pathogen.

Our study has detected several rare Gram positive and Gram negative isolates which are either not detected by conventional biochemical methods or considered as contaminants by several authors if ever they try to detect them through automated methods. Few authors have designated these rare organisms as pathogens proving them to be agents responsible for BSI in immuno compromised patients.[9]

Our study has detected usual pathogens like *S.aureus, Enterococcus* spp, *Streptococcus* spp, *Eschrechia coli, Klebsiella pneumonia, Salmonella typhii* and *paratyphii, Pseudomonas aeruginosa, Burkholderia* spp and *Acinetobcter baumanni.* At the same time we have also detected rare pathogens like *Kocuria*[12], *Leuconostoc mesenteroides*[13], *Micrococcus luteus*[14], *Alloiococcus otitis*[15], *Aerococcus viridans*[16], *Proteus* spp, *Enterobacter spp*[17], *Pantoea agglomerans*[18], *Serratia marcescens*[19], *Yersinia enterocolitica*[20], *Salmonella enterica*[21], *Peudomonas stutzeri*[22], *Acinetobacter lwoffi, Sphingomonas paucimobilis*[23], *Stenotrophomonas maltophila*[24], *Ralstonia mannitollytica*[25], *Achromobacter* spp[26], *Roseomonas gilardii*[27], *Comamonas testosterone*[28], *Aeromonas caviae*[29], *Cronobacter dubiliensis*[30], *Methylobacterium*[31] *and Brucella mellitensis.*[32]

We have also reported CoNS and Diphtheroids as pathogens, which are normally considered as skin commensals and common contaminants of blood. Some studies also consider *S.maltophila* and other rare pathogens as contaminants of blood samples[33] while other studies have detected the same as important blood borne pathogens.[7]

All the fungal isolates that included *Candida* (96.5%) and *Cryptococcus neoformans* (3.4%) are proved pathogens. *Candida* species other than *albicans* (64.2%) pre-dominated *Candida albicans* (35.7%) in our study. This change in epidemiology could be associated with severe immunosuppression or illness, prematurity, exposure to broad-spectrum antibiotics and older patients.[34]

We processed each and every isolate and identified it upto the species level. Once the isolate was identified we searched the published literature regarding that isolate and prepared notes that were dispatched along with the culture and sensitivity reports.

Following notes were prepared/can be prepared (with reference to some unusual/rare and emerging blood borne pathogens) after searching the literature thereby highlighting special features related to the isolated organism.

The isolated Gram positive bacteria are considered as culture contaminants but have been associated with human infections including bacterimea. Most of these are widely distributed in environment and have been recovered from dust, vegetable, dairy products and different hospital areas like intensive care units, treatment rooms, delivery and recovery rooms. Few of these are commensals on human skin, mucosa, oral cavity and oro pharynx. They have been recently recognised as opportunistic pathogens among Immuno compromised and immuno suppressed hosts due to the use of intravascular devices, antibiotic prophylaxis and evolution of chemotherapeutic agents and hence are implicated in recurrent bacterimea. A handful of these pathogens are intrinsically resistant to multiple antibiotics with limited treatment options.[12-16] The isolated Gram Negative Bacilli are the Members of Enterobacteriaceae that have taken on clinical significance as opportunistic nosocomial pathogens especially among intensive care patients. These ubiquitous organisms are widely encountered in terrestrial and aquatic environments including water, soil, sewage and stool. They occur as commensal micro flora in the intestine of humans and animals. They tend to contaminate various medical, intravenous and other hospital devices including operative cleaning solutions. Due to their prevalence in the body, these organisms mostly affect the vulnerable age groups such as elderly & young and can cause prolonged hospitalization. Some of these are the common causes of hospital infections among immune compromised individuals on exposure to contaminated fluids and equipments. Most of these have ability to form bio-films and considerable amounts of cytotoxins. They usually harbor Multi Drug Resistance (MDR) mechanisms that can complicate treatment decisions.[17-21]

The isolated Gram Negative bacteria are the members of Non-Fermenter that are infrequently isolated from clinical samples. These ubiquitous organisms grow well in moist environments such as soil, water and plants with minimal nutrient resources. They are of low clinical virulence but innate and multi-drug resistance is frequently reported among them. They are commonly responsible for hospital outbreaks associated with contaminated saline solutions, intravenous fluids, antiseptics and disinfectants. The infections are common among immuno-compromised, immunosuppresive and elderly population. They have been described or

reported as an aggressive opportunistic and emerging life threatening pathogens. Sometimes polymicrobial flora involving these organisms has been reported to cause bacteremia.[22-32]

Useful lessons learned after analyzing the etiology of BSI helps to understand the severe illnesses and the causative agents constantly associated with the disease. The identification of isolates further helped in selecting the list of drugs to be tested in manual AST methods or selecting the AST cards in case of automated AST detection methods.

CONCLUSIONS

The reason for undertaking this study and the selected article title is not merely to make a list of organisms isolated from blood samples but to give a serious thought whether to consider these organisms as pathogen or a commensal. Because, in laboratories where large number of blood samples are processed we are not just getting the samples from immuno compromised or immuno suppressed patients. Also we don't have the complete history of patients in several cases. So through this, what we suggest is just to process each and every sample that has flagged positive by BacT alert and identify every isolate so that we can proceed to determine their antibiotic sensitivities.

Once the identified organism seems to be an unusual one, then the consultant microbiologist should go through literature and published articles for the detailed knowledge of their basic and special features, habitat and clinical correlation. They are supposed to prepare a short note highlighting all the important features related to an isolate and attach that note with the main report. We suppose that this would help clinician to correlate the report in a much better way. Sometimes the isolated organism is found to be some unusual species of a usual organism with totally different name. Hence it is essential for the microbiologist to make the clinician aware about the originality and severity of an isolated organism so that he or she can proceed for the empirical therapy in the absence of sensitivity reports.

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