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Evaluation the Pattern of BSI in Cancer Patients and Their Sensitivity and Resistance toward Antibiotic

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Abstract

Background: Bloodstream infections (BSIs) account for large-scale morbidity and mortality among cancer patients requiring a rational antibiotic policy. In Bangladesh, there is a paucity of data regarding incidence and pattern of BSI in such patients. Objective: To evaluate the pattern of BSI in cancer patients and their sensitivity and resistance toward antibiotic. **Material & Methods:** The present study was a retrospective analysis of BSI patterns among various cancer patients treated at Department of Oncology, Enam Medical College Hospital, Saver, Bangladesh during the period from January to June 2021. Blood culture results and their sensitivity patterns of these cancer patients along with the demographic characteristics were collected from the records and maintained in the structured pro forma. Before starting empirical antibiotics, 10 ml of blood was collected into Bract/ALERT culture media. **Results:** A total of 82 patients/episodes had confirmed BSI. Gram-negative bacteria accounted for 43 (52.4%) cases, followed by Gram positive 38 (46.4%) cases and 1 case of candida species. The most common organisms isolated were Klebsiella pneumonia and Staphylococcus aureus consisting of 17 cases each. The Gram-negative bacterial isolates (n = 43) were sensitive to cefoperazone plus sulbactam, piperacillin plus tazobactam, carbapenem, and colitis in 18 (41.9%), 19 (44.2%), 29 (67.4%), and 40 (93%) episodes, respectively. The sensitivity of Gram-positive bacteria (n = 38) to vancomycin, linezolid, and teicoplanin was seen in 37 (97.3%), 37 (97.3%), and 35 (92.1%) episodes, respectively. Multidrug-resistant bacteria accounted for 17 (39.5%) cases of Gram-negative isolates and 9 (53%) of which were K. pneumonia. Extended spectrum beta-lactamase activity was seen in 11 of 26 episodes of Enterobacteriaceae. Four of 17 S. aureus and 3 of 11 coagulase-negative Staphylococci were methicillin resistant, and 1 of 2 cases of Enterococcus was vancomycin resistant. **Conclusions:** Gram-negative bacteria are the predominant cause of BSI in cancer patients and development of a high degree of resistance to commonly used antibiotics is challenging.

Keywords:- Antibiotic sensitivity, blood stream infections, cancer, resistance.

INTRODUCTION

Cancer patients are prone to infections, which increases the duration of hospital stay and cost of care. As per the data from the Infectious Diseases Society of America (IDSA), 10%– 25% of cases of febrile neutropenia in cancer patients have documented bacteremia.[1] Bloodstream infections (BSIs) are frequently encountered in patients presenting with neutropenic fever. BSI was implicated in 6%–23% of all cases of febrile

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neutropenia across multiple Indian studies.[2,3,4,5] It is an important cause of morbidity and mortality among cancer patients with the crude mortality rates between 18% and 42%.[6] Blood culture is the cornerstone in the management of febrile neutropenia and facilitates the identification of causative organism with antibiotic susceptibility pattern. BSIs caused by Gram-negative rods are associated with high mortality. Hence, prompt empirical antibiotic therapy active against these organisms is warranted.[7] Blood culture should be sent immediately prior to initiating antibiotic therapy. In the last few decades, the alarming rise in the incidence of multidrug-resistant (MDR) bacteria has posed a challenge in treating BSI.[8] The patterns of antibiotic sensitivity of BSI are variable. Hence, a rational institutional antibiotic policy is of paramount importance. With this background, the present study was conducted to retrospectively analyze antibiotic sensitivity and resistance pattern of different organisms isolated on blood culture positive cancer patients.

MATERIAL AND METHODS

The present study was a retrospective analysis of BSI patterns among various cancer patients treated at Department of Oncology, Enam Medical College Hospital, Saver, Bangladesh during the period from January to June 2021. Blood culture results and their sensitivity patterns of these cancer patients along with the demographic characteristics were collected from the records and maintained in the structured pro forma. Before starting empirical antibiotics, 10 ml of blood was collected into BacT/ALERT culture media. Samples were incubated in the automated Bract/ALERT 3D system (BIOMERIEUX, USA) and BACTEC 9050 (BD BancTec™ 9050 Blood Culture System) for a minimum of 7 days before labeling the results as negative. Further, characterization of all blood culture-positive samples was done by subculture on blood agar, chocolate agar, and MacConkey agar media and direct Gram's staining. The VITEK®2 system (bioMérieux) was used for identification and antimicrobial susceptibility testing of bacteria grown in standard aerobic blood culture bottles. In our institution, cefoperazone plus sulbactam (CFS) is the first-line antibiotic for patients admitted with febrile neutropenia. In hematologic malignancies, amikacin is added. Piperacillin plus tazobactam (TZP) and meropenem are used in the 2nd and 3rd lines, respectively. For patients presenting with hemodynamic instability, severe oral microsites, skin and soft tissue infection, and suspected central line infections, teicoplanin is added for Gram-positive coverage. Caspofungin is used in case of persistence of fever beyond 72 h in spite of adequate Gram-negative and Gram-positive coverage.

All data were presented in a suitable table according to their affinity. A description of each table and graph was given to understand them clearly. All statistical analysis was performed using the statistical package for social science (SPSS) program, and Windows. Continuous parameters were expressed as mean±SD and categorical parameters as frequency and percentage. Comparisons between groups (continuous parameters) were made by Student's t-test. Categorical parameters compared by Chi-Square test. The significance of the results as determined by a 95.0% confidence interval and a value of $P<0.05$ was considered to be statistically significant.

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RESULTS

A total of 82 episodes of blood culture positivity were detected during the study period. The different microbial organisms isolated from blood culture with their incidence were depicted in Table 1. Gram-negative bacteria were found to be the predominant cause of BSI consisting of 43/82 episodes (52.4%), followed by Gram-positive bacteria, i.e., 38/82 episodes (46.4%), and only one episode of candidemia (1.2%) detected. Klebsiella pneumonia was the most common organism isolated among Gram-negative bacteria, i.e., 17/43 episodes, and Staphylococcus aureus was the most common organism isolated among Gram-positive bacteria, i.e., 17/38 episodes. Sp.: Single species, spp.: Multiple species, CoNS: Coagulase-negative Staphylococci, K. pneumoniae: Klebsiella pneumoniae, E. coli: Escherichia coli, P. aeruginosa: Pseudomonas aeruginosa, A. caviae: Aeromonas caviae MDR was seen in 17 (39.5%) episodes of Gram-negative BSI (n = 43). MDR isolates were K. pneumoniae (9/17; 52.9%), Pseudomonas aeruginosa (3/7; 42.9%), Acinetobacter (2/6; 33.33%), Escherichia coli (2/9; 22.22%), and Fusobacterium species (1 case). Extended-spectrum beta-lactamase (ESBL) activity was seen in 11 out of 26 (42.3%) episodes of Enterobacteriaceae, of which 9 were K. pneumoniae and 2 were E. coli. The overall rate of incidence of methicillin-resistant S. aureus (MRSA) was 4.88% (4/82), which was 23.53% when compared with all S. aureus isolates. Similarly, methicillinresistant coagulase-negative Staphylococci (CoNS) had the overall incidence rate of 3.66% (3/82), which was 27.27% of episodes among all CoNS isolates. Only 1 (1.22%) episodeofvancomycin-resistant Enterococcus (VRE) was found among total BSI episodes. The antibiotic sensitivity patterns among different Gram-negative and Grampositive isolates are depicted in Tables 2 and 3, respectively. Only 18/43 (41.9%) and 19/43 (44.2%) of Gram-negative bacteria were sensitive to CFS and TZP antibiotics, respectively. The sensitivity of carbapenem and colistin was seen in 29/43 (67.4%) and 40/43 (93%) Gram-negative isolates, respectively. Hence, we found relatively less sensitivity to commonly used antibiotics for Gram-negative organisms. The sensitivity of Gram-positive bacteria to vancomycin, linezolid, and teicoplanin was seen in 97.3% (37/38), 97.3% (37/38), and 92.1% (35/38) of episodes, respectively. Results are expressed as a percentage of the number of isolates in each group. CTX: Cefotaxime, CRO: Ceftriaxone, CFS: Cefoperazonesulbactam, CEF: Cefepime, TZP: Piperacillintazobactam, MERO: Meropenem, IMI: Impanel, K. pneumonia: Klebsiella pneumonia, E. coli: Escherichia coli, P. aeruginosa: Pseudomonas aeruginosa.

Table 1: Incidence of different organisms isolated on blood culture (n=82)

Microorganisms isolated	**N (%)**
Gram-negative bacteria	
K. pneumonia	17 (20.7)
E. coli	9 (11)
P. aeruginosa	7 (8.5)
Acinetobacter spp.	6 (7.3)

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Enterobacter sp.	2 (2.4)
A. caviar	1 (1.2)
Fusobacterial sp.	1 (1.2)
Gram-positive bacteria	
S. aureus	17 (20.7)
Cons	11 (13.3)
Streptococcus spp.	8 (9.5)
Enterococcus sp.	2 (2.4)

Table 2: Antibiotic sensitivity patterns of the Gram-negative bacteria (N=82).

Organism (n)	CTX/CRO	CFS	CEF	TZP	Amikacin	IMI/MERO	Colistin	Tigecycline
	%	%	%	%	%	%	%	%
K. pneumonia (17)	11.7	35.2	29.4	35.2	29.4	58.8	88.2	70.5
E. coli (9)	11.1	55.5	66.6	55.5	66.6	77.7	100	66.6
P. aeruginosa (7)	0	42.8	42.8	42.8	57.1	71.4	85.7	28.5
spp.(6)	16.6	33.3	66.6	50	50	66.6	100	66.6
Enterobacter spp.(2)	0	50	50	100	100	100	100	50
Fusobacterial spp.(1)	0	0	0	0	0	0	100	0
Aeromonads spp.(1)	0	100	100	100	100	100	100	100

Table 3: Antibiotic sensitivity patterns of the Gram-positive bacteria (N=82)

Organism (n)	Erythromycin	Ciprofloxacin	Gentamicin	Vancomycin	Teicoplanin	Linezolid
	(%)	(%)	(%)	(%)	(%)	(%)
S. aureus (17)	35.3	47	88.2	100	88.2	100
Cons (11)	27.3	45.4	45.4	100	100	100
Streptococcus spp.(8)	75	75	NA	100	87.5	100
Enterococcus spp.(2)	0	0	50	50	100	50

Results are expressed as a percentage of the number of isolates in each group. CoNS: Coagulase-negative Staphylococci, spp.: Multiple species, S. aureus: Staphylococcus aureus, NA: Not applicable.

DISCUSSION

The assessment of pattern of infections and antibiotic sensitivity is important in modulating antimicrobial policy to reduce infection-related morbidity and mortality. In the present study, we determined the predominant isolates causing BSI in cancer patients and their antibiotic sensitivity patterns. There is a paucity of data regarding the pattern of BSIs in cancer patients. The incidence of blood culture positivity in cancer patients presenting with fever has a variability in the range of 6%–23% across multiple Indian studies.[2,3,5,8,9,10] Such variability in the incidence could be due to patient-related factors such as type of cancer patients taking treatment, prior exposure to antibiotics, and use of central venous catheters

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and technical factors related to collection and inoculation (inadequate and faulty blood sample collection and the time lag between collection and inoculation). There is a change in the incidence of organisms isolated from BSI in cancer patients over time. There is an increase in the prevalence of Gram-positive bacteremia over Gram-negative bacteremia, particularly in developed countries, in febrile neutropenic patients over the last three decades, and the reports suggest that 70%–81% of the bacteria isolated from BSI are Gram positive.[6,11,12,13,14] This is due to the increased use of central venous catheters, fluoroquinolone prophylaxis, aggressive antineoplastic regimes causing severe oropharyngeal microsites and bowel damage, and H2 receptor blockers.[10,15] We found Gram-negative rods as the predominant cause of BSI among cancer patients and the cause could be due to relatively lower use of indwelling catheters and other portal devices. Most of the studies done in Bangladesh and other developing countries also found predominance of Gram-negative bacilli in febrile neutropenia.[10,11,16,17,18,19] The data on BSI from studies done in Bangladesh along with the most common organism isolates and their antibiotic sensitivity pattern are depicted in.[2,5,6,8,10,11,16,17,18,19] Among the Gram-negative bacteria, E. coli followed by K. pneumonia are most commonly isolated and together account for 18%–43% of all BSIs. S. aureus has consistently been the most common Gram-positive bacterial isolate, although there is an increasing trend in Cons infections in cancer patients. The results from our study show both K. pneumonia and S. aureus as the most common cause of BSI. Most Gram-negative bacteria are resistant to commonly used antibiotics with variable sensitivity across different strains. The sensitivity for beta-lactams/beta-lactamase inhibitors vary approximately between 13% and 65%, with K. pneumonia being the most resistant.[6,10,11,16,17,18,19] In our study, there was no difference found in sensitivity between CFS and TZP. Different studies from Bangladesh showed higher sensitivity of E. coli among Gram-negative bacteria to amikacin (76% to 86% isolates).[6,10,11,17,18,19] A study by Babu et al. showed a resurgence of strains resistant to CFS, but sensitive to ceftazidime plus amikacin probably due to the routine use of CFS in first line at their center.[10] Sensitivity to carbapenems ranged between 17% and 83%, with K. pneumonia being the most resistant and E. coli being the most sensitive.[10,11,16,17,18,19] Almost all strains were uniformly sensitive to colitis. Babu et al., Agrawal et al., and Thacker et al. in their studies found colitis sensitivity in 100%, 100%, and 97% cases, respectively.[10,16,19] We also found that majority of Gram-negative strains were sensitive to colitis. MDR is defined as per the guidelines by the European Centre for Disease Prevention and Control (ECDC) and the Centers for Disease Control and Prevention expert pan.[20,21] More recent data show very high incidence of MDR Gram-negative bacteria in the range of 35%–64% among all the isolated strains.[10,16] We also found MDR organisms in 39.5% of Gram-negative bacteria based on the ECDC guidelines supporting the literature. We found 9/17 (52.9%) of K. pneumonia, 2/9 (22.2%) of E. coli, 3/7 (42.9%) of P. aeruginosa, 2/6 (33.3%) of Acinetobacter spp., and 1 case of Fusobacterial species as the constituents of MDR. The overall incidence of MRSA was 4.88% and VRE was 1.22% in our institute. The incidence of MDR bacterial infection has grown manifold in the last few years. In a study by

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Jernigan et al. between 2012 and 2017, the incidence of MDR bacteria in all hospitalized US patients decreased for MRSA infection, VRE infection, carbapenem-resistant Acinetobacter species infection, and MDR P. aeruginosa infection. The incidence of carbapenem-resistant Enterobacteriaceae infection remained stable. However, there was a sharp increase in the incidence of ESBL infection by 53.3%.[22] ESBL-producing Enterobacteriaceae accounted for 15% of all isolates from a study in 2007, with 63% of Klebsiella spp. and 51% of E. coli being ESBL producers.[6] We found higher ESBL activity among Enterobacteriaceae, i.e., 42.31% of cases (52.9% of K. pneumonia and 22.2% of E. coli). However, confounding factors coexist in our study such as limited number of sample size. The incidence of MRSA in comparison is low and lies in the range of 8%–33%.[10,23] Agrawal et al. reported 3 out of 6 Cons to be methicillin resistant.[16] Praha's et al. reported 50% incidence of VRE in their study.[6] Methicillin-resistant Cons is an emerging pathogen in BSI in cancer patients, accounting for more than 50% resistance rates across many European countries.[24] We found the overall incidence of MRSA and methicillin-resistant Cons in 4.88% and 3.66% of BSI episodes, respectively. Given a high degree of resistance to frontline drugs (CFS/ TZP), a de-escalation strategy incorporating the most sensitive antibiotics (e.g., carbapenems or colitis) first with step down in case no BSI is detected in next 72 h is worthy of consideration. This strategy has been successfully utilized in febrile neutropenic patients who present in severe sepsis where time is of great essence. Many of these patients have previous infection or colonization by MDR bacteria. De-escalation approach can also be useful in centers with high frequency of ESBL bacteria.[20] The limitations of our study lie in its retrospective nature with inadequate data on the clinical profile of the cancer patients for whom samples were sent. At the time this study was conceived, minimum inhibitory concentration was not being done routinely in our laboratory.

CONCLUSIONS

We found Gram-negative bacteria as the predominant cause of BSI in cancer patients. There is a relatively higher incidence of S. aureus. Strict hand hygiene and meticulous care of CVCs is vital in preventing such infections. Klebsiella pneumonia was the most common MDR organism; most of the isolates were sensitive to colitis. De-escalation strategy may be utilized for sick patients who have had prior growth with ESBL Enterobacteriaceae. Periodic assessment of the clinical variables and microbial data is important to form an antibiotic-prescribing policy to avoid irrational use of antibiotics and their resistance. The benefit of empiric antibiotic treatment in context of rising bacterial resistance among febrile neutropenia patients' needs to be confirmed and should be tailored according to the locally prevalent pathogens with their susceptibility patterns.

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