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Review Article

Microbiological etiology and management approach of febrile neutropenia

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ABSTRACT

Many etiologies have been proposed to predispose neutropenic fever, and infections have been reported in less than one-third of the reported cases. However, etiologies might have a significant impact on the prognostic, and can even lead to mortality. In this literature review, the aim to discuss the different microbiological etiologies of neutropenic fever, and the management approaches of such conditions, including the proper assessment and evaluation of patients. Additionally, the goal of this literature review to discuss the appropriate treatment and prophylaxis measures based on the assessment results. Many bacterial pathogens could be isolated from patients suffering from neutropenic fever, including both the gram-positive and negative organisms, such as pseudomonas aeruginosa, E. coli, Klebsiella spp, actinobacteria spp, in addition to many other bacteria such as staph. Nevertheless, Aureus was commonly isolated from the infected patients, and it has been reported with increased morbidity and mortality rates. Assessment of the severity of the condition and identification of the microbiological activity can significantly lead to enhance management of the infected patients. Detailed information about the etiology and management are provided within the main text of this study. Further efforts are needed to increase awareness related to the hazards of the inadequate and incomplete assessments of patients with neutropenic fever, which might lead to delayed or inadequate management and worsened prognosis.

Keywords: Microbiology, Management, Culture, Neutropenic fever, Critically ill

INTRODUCTION

Following the administration of chemotherapy for solid tumors, and many hematological malignancies, neutropenic fever can be observed as a significant complication, which has been reported in up to 80% of the infected patients.[1,2] Although many recent medical advances have been developed. For example, febrile neutropenia can significantly lead to many burdens as increased secondary costs to a prolonged hospital stay of patients. Also, it reduced the effectiveness of the administered chemotherapy, and worsened prognosis leading to potentially elevated morbidity and mortality rates.[3] Moreover, many etiologies have been proposed to

predispose neutropenic fever, and infections have been reported in less than one-third of the reported cases. However, etiologies might have a significant impact on the prognosis, and it can even lead to mortality.[4] Bacterial infections are the most common ones. However, fungal and viral infections have also been previously noticed.[5] The development of bacteremia and sepsis in infected patients might lead to significant complications, as previously reported that septic shock and sepsis can develop in up to 30% of patients.[1,6-9] Therefore, adequate management is urgently needed. In this study, the aim to discuss the microbiological etiology of neutropenic fever, and the current management approaches, according to the evidence obtained from studies in the literature.

METHODS

This literature review is based on an extensive literature search in Medline, Cochrane, and EMBASE databases on 17th June 2021 using the medical subject headings (MeSH), and a combination of all possible related terms. This was followed by the manual search for papers in Google Scholar and the reference lists are included at the end of this research.[10,11] Papers discussing neutropenic fever were screened for relevant information. We did not pose any limits on date, language, age of participants, or publication type.

DISCUSSION

Microbiological etiology

The presence of infections in the blood of patients suffering from neutropenic fever can significantly worsen the prognosis and may end up with mortality. It is worth mentioning that studies in the literature have indicated that the microbiological etiology of neutropenic fever has significantly changed over time. For instance, gram-negative bacterial pathogens were reported as the most commonly isolated during the period from the 1960s-1970s while in recent decades, it has been noted that gram-positive bacteria are becoming more common, which is probably due to the increased overuse of antibacterial interventions. However, this point remains controversial among the different studies in the literature. For instance, a previous investigation by Mandal et al reported that the prevalence of gram-positive and negative isolates was 34.61% and 61.53%, respectively.[12] Besides, *Pseudomonas aeruginosa* followed by *methicillin-resistant Staphylococcus aureus*, *Acinetobacter species*, *Escherichia coli*, *coagulase-negative Staphylococcus*, *methicillin-sensitive S. aureus*, and ESBL *E. coli* were the commonest bacterial isolates among their included patients with febrile neutropenia with estimated prevalence rates of 14.1%, 12.82%, 11.53%, 10.25%, 8.97%, 8.97%, 6.41%, and 6.41%, respectively. The authors also reported that other etiologies were also observed, such as *Citrobacter kosseri, Ralstonia paucula, Citrobacter freundii, Cedecia neteri* and others. However, they come at lower frequencies than the aforementioned bacterial isolates, and candida was also noticed in two isolates belonging to two patients. The high prevalence of pseudomonas in this study, which is a highly resistant organism that might be attributable to the high prevalence of the organism in the clinical settings where the study was conducted. In this context, it was previously reported that pseudomonas species account for up to 50% of the microbiologically-induced febrile neutropenia, which was also reported with an overall worldwide mortality rate of 10%.[13-17] These results were indicated in another big Indian investigation, which reported that Acinetobacter spp. and Pseudomonas aeruginosa were the most commonly isolated pathogens from patients suffering from neutropenic fever secondary to bone marrow failure and hematological malignancies and reported bacterial resistance. This led to worsened prognosis for many of these cases, which were significantly associated with further bacterial resistance and complicated management.[18] Another investigation by Paul et al also indicated that gram-negative organisms were the most commonly isolated in their patients' cultures and *Klebsiella* spp. was the commonest isolate among others.[19] It has been previously demonstrated that among patients with neutropenic fever, gram-negative bacteria represent around two-thirds of the isolated cultures in these patients globally.[13,14,20-22] Although candida species are not commonly observed in patients with febrile neutropenia, previous investigations have demonstrated that they are the 4th most commonly isolated pathogens from the patients' blood within the intensive care units.[23,24] This indicates the increasing burden of fungal infections that can significantly worsen the prognosis of critically ill patients, requiring integrated approaches to adequately treat such phenomena. It has also been previously estimated that around 80% of the microbiological etiologies of neutropenic fever are attributable to the presence of Coagulase-negative Staphylococcus, in addition to viridian's streptococci. Studies have also reported that Coagulase-negative Staphylococcus are the main universal causes of infections.[25-28] Interestingly, bacteriemia secondary to staphylococcal infections has been reported with reduced mortality rates, while oral infections by streptococci have been estimated to be direct causes of neutropenic fever in 39%, with estimated higher mortality rates of 4-22% among the different studies in the literature.[29-31] Karanwal et al reported that staphylococcus aureus was the most commonly isolated gram-positive pathogen while *E. coli* was the commonest gram-negative organism among others, which have been reported to be more common than the gram-positive bacteria.[32]

Management approaches

Assessment of patients

At first, adequate evaluation of the case should be determined for accurate management, and prevention of recurrence among these cases in the future. All the relevant laboratory functions should be adequately assessed to determine the appropriate treatment modality. A complete blood picture should be performed for the patient to

determine the severity and levels of neutropenia. Besides, urinalysis, blood, and throat cultures should also be performed to determine the source of the infections and the causative organism. This step is essential before initiating any treatment modality, especially the ones based on the administration of empirical therapies and intravenous broad-spectrum antibiotics, and accordingly, culturing should be done at the frequently suspected sites of infections as the installed catheters, in addition to the venous sample that should always be withdrawn. Besides, having a previous history of a certain infection, for instance, urinary tract infections, is an indicator to receive adequate management of such conditions, even if they were asymptomatic.[33] In the same context, stool examination should be performed if gastrointestinal tract-related symptoms as diarrhea were present, and chest investigations as X-ray should also be performed if the patient suffers from respiratory-related illnesses. Furthermore, assessment tools to adequately evaluate the underlying conditions of the affected patients have been reported in the literature, and the Clinical Index of the Stable Febrile Neutropenia (CISNE), and the Multinational Association for Supportive Care in Cancer (MASCC) are two common modalities that are being commonly used in the clinical settings for risk stratification of patients suffering from febrile neutropenia into high and low-risk groups. It has been previously reported that the CISNE can be more specific than the MASCC assessment tool and can be better and effectively used to assess patients with neutropenic fever within emergency settings.[5] Another advantage of this tool is that it contains the domains of the Eastern Cooperative Oncology Group (ECOG) Performance Status, which allows for adequate assessment and evaluation of the patient's underlying functional status, and ability to receive medical therapy in case of severe illness, in addition to the usual risk stratification of the condition. The score is composed of seven main domains that should be evaluated and given a score as follows: assessment of the ECOG performance status and is given a score of 2, evaluating the presence of chronic obstructive pulmonary disease and is given a score of 1, evaluating the presence of cardiovascular chronic disease, with a score of 1, assessment of the presence of stress-related hyperglycemia, with a score of 2, evaluating any potential development of mucositis, which should be considered with a score of 1 if the condition is graded with grade 2 or higher, if the monocytes count is <200/mcL, a score of 1 should be given, and interpretation of the previous steps. Finally, based on the cumulative score, clinicians should be able to determine whether patients should be treated within the outpatient clinics (score= 0-2) or should be hospitalized (score ≥3). On the other hand, the MASCC scoring system is usually used to assess the severity of the condition and the potential presence of complications, and patients are assessed on a maximum score of 26, as patients having a score that is >21 are interpreted as having a low-risk disease, while patients having a score that is <21 are high-risk groups.[34] No or mild symptoms were given 5 marks, severe symptoms were given 0, while moderate was given only 3. No presence of hypotension was given 5 and no presence of COPD was given 4. According to the type of cancer, grading of these patients could be also conducted. Solid tumors are given 4, hematological tumors or lymphoma with the previous history of fungal infections are given 4, a 4 was also given to the degree of dehydration, 3 to the status on admission, and 2 if the patient's age was <60 years old. These indices should be used before starting the treatment plan.

Treatment and prevention

It has been previously demonstrated that the administration of clavulanate/amoxicillin, in addition to fluoroquinolone, empiric therapy, and symptomatic management is recommended for patients suffering from a mild condition, with no need to be hospitalized (Figure 1).[35] For patients having any form of allergies against penicillin, clindamycin should be indicated in such cases. This management modality should only last for 2-3 days. After that, if the case is still febrile, the patient should be admitted to the hospital.[5] On the other hand, patients suffering from a severe condition or having a high risk to develop it should be treated following triage by one hour with an intravenous administration of antibiotic therapy. Observation of such cases should be conducted for at least four hours before being discharged from the hospital. Moreover, anti-pseudomonal beta-lactam therapeutic drugs should be administered as a monotherapy for these cases, and the group might include many modalities as carbapenems, cefepime, tazobactam, and piperacillin as indicated by a previous report from the Infectious Disease Society of America.[5] It was also previously reported that vancomycin administration is not recommended in such cases; however, if catheter-related infections, pneumonia, soft-tissue of skin-related infections were suspected, or if the patient was hemodynamically unstable, it is recommended that vancomycin therapy should be inaugurated.[36] If the cases were observed to be resistant to the different management modalities or no enhancements in the case were noticed, different approaches and therapeutic modalities should be approached.[5,37-41] For instance, linezolid, vancomycin, and daptomycin should be administered for methicillin-resistant Staphylococcus aureus, daptomycin and linezolid should be administered for vancomycin-resistant enterococci, carbapenem should be administered for Extended-spectrum beta-lactamase-producing organisms, and polymyxin, carbapenems, tigecycline, or colistin should be administered for *Klebsiella* pneumoniae-related infections.

For proper management to be adequately done, proper prevention should also be approached for these patients to enhance the prognosis. Many previous recommendations have been published and reported that various interventional approaches should be used in such conditions. For instance, in patients that have a high risk of developing the condition, fluoroquinolones should be administered.

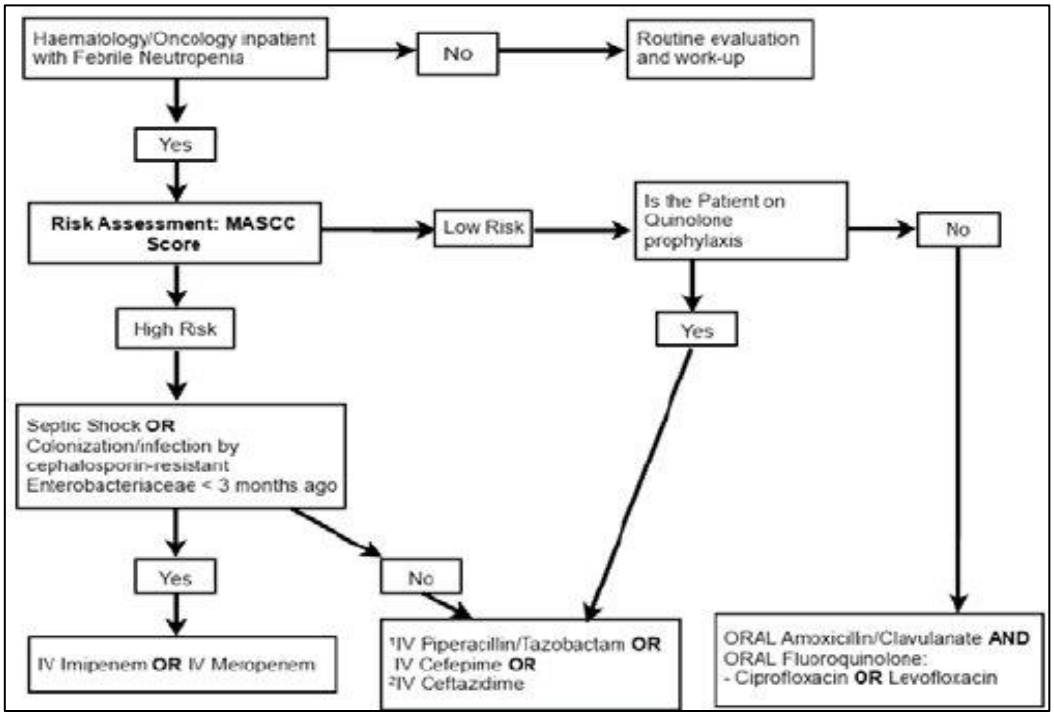

Figure 1: An algorithm for managing patients with febrile neutropenia.[43]

For patients suffering from profound neutropenia, oral triazole and antifungal therapy should be inaugurated. For prophylaxis against *Pneumocystis jirovecii*- induced pneumonia, trimethoprim-sulfamethoxazole has been recommended in such situations when patients tend to have a risk of developing the condition by more than 3.5%. Prophylactic annual administration of influenza vaccines should also be approached for all of the relevant patients that are indicated to receive chemotherapy. For patients that were previously infected with the hepatitis B virus, prophylaxis against reactivation should be done by prescribing nucleoside reverse transcription inhibitor. Besides, prophylaxis should also be conducted for patients undergoing leukemia-induction therapy, or hematopoietic stem cell transplantation and who tend to have a great risk of catching a herpes-simplex viral infection or are seropositive. Furthermore, it was previously demonstrated that for any patients that have been indicated to be at a high risk of developing febrile neutropenia, granulocyte-colony stimulating factors should be administered by these patients according to the recent recommendations by the National Comprehensive Cancer Network.[42]

CONCLUSION

This literature review has discussed the different microbiological etiologies of neutropenic fever, in addition to the management approaches of such conditions, including the proper assessment and evaluation of patients, in addition to the appropriate treatment and prophylaxis measures based on the assessment results. Many bacterial pathogens could be isolated from patients suffering from neutropenic fever, including both the gram-positive and negative organisms. *Pseudomonas aeruginosa*, *E. coli*, *Klebsiella spp*, *actinobacteria spp*, in addition to many other bacteria as *staph. aureus* was commonly isolated from these patients and has been reported with increased morbidity and mortality rates. Assessment of the severity of the condition and identification of the microbiological activity can significantly lead to enhance management of these patients.

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