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BACTERIAL INFECTIONS IN NEUTROPENIC CANCER PATIENTS: EPIDEMIOLOGY, CHANGING PATTERN AND ANTIMICROBIAL PROPHYLAXIS

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Abstract:

Cancer patients are at higher risk of infection due to altered immune system caused by aggressive chemotherapy. Neutropenia is a most common adverse effect of such types of therapeutics regimes. Neutropenic patients develop serious life-threatening infection caused by both gram positive and negative bacteria. Febrile neutropenia and bacteremia are serious infectious condition in neutropenic cancer patient after receiving cytotoxic chemotherapy. The major changes have been witnessed in pathogens with respect to epidemiology and drug resistance at national and international level. The changing pattern of pathogens, rapid development of bacterial resistant and emergence of new clinical problems imposed extra burden on clinicians to manage neutropenic cancer patients. It is therefore imperative that microbiological profile for antibiotic sensitivity pattern is known before empirical or therapeutic use of antibiotics.

Key words: Cancer, Neutropenia, Infection

1. Introduction:

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Bacterial infection is a major complication and cause of morbidity and mortality in neutropenic cancer patients [1]. Cancer patients are at higher risk for bacterial infection due to compromised immune system caused by intensive chemotherapy. Increase use of aggressive chemotherapeutic regimes for the treatment of cancer has resulted in increasing number of these patients experiencing the profound neutropenia. These regimes depress the normal functions of bone marrow resulting in decease of number of white blood cells, red blood cells and platelets in circulating blood thus patients become immunocompromised and susceptible to infection [2]. Bodey et al described that a patient with history of cancer illness, medical complications and development of serious infections along with neutropenia recognized as under risk [3].

Administration of empirical antimicrobial broad spectrum antimicrobial therapy is immediately required to cover majority of bacterial pathogens encountered in this setting. Considerable changes in pathogens causing infection in cancer patients has been recognized at national and international levels. Therefore continuously surveillance of locally prevalent pathogens and their sensitivity pattern is essential to improve treatment outcomes and prolonged survival in cancer patients with neutropenia.

- **Fever and infection in cancer patients:**

Infection or manifestation of basic neoplastic disease is a constant concern [7]. Briggs describe that intermittent fever is a symptom of cancer. This fever might be due to an infection or any known complication of underlying disease [8]. Hughes et al reported that fever 48-60% of neutropenic patients who have fever establish an infection. Approximately 20-25% neutropenic cancer patients had fever due to unknown origin. Such episodes are termed as unexplained fever and a very small portio-n (5%) of febrile patients develop fever due to complication of cancer [9, 10].

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Infection is major cause of death in patients suffering from malignant blood diseases. Approximately 80% of patients who had leukemia had multiple episodes of infection during the course of disease [11]. Bloodstream infections are the most serious complication in neutropenic cancer patients. Bacteremia defines as the invasion of pathogenic bacteria in bloodstream and it can be recognized by blood culture. The isolated pathogens are given etiology significance based on clinical and microbiological assessment [12]. The major causes of Bacteremia in hematological malignancies are long hospitalization, dose reduction and delay in antimicrobial chemotherapy treatment [13,14]. Bacteremia is caused by both gram positive and negative bacteria and it is grouped according to bacterial isolates and origin of the bacteremia. The other sites of infection in neutropenic cancer patients are skin, urinary tract, respiratory and gastrointestinal tract [15-20].

- **Common bacterial pathogens:**

Among gram positive bacteria coagulase negative Staphylococcus (CoNS), *Staphylococcus aureus, Enterococcus faecalis, Streptococcus viridans, Streptococcus pneumoniae* and beta hemolytic streptococci are frequently isolated from neutropenic cancer patients [21-22]. Patients those undergoing chemotherapy and develop severe mucosititis are at higher risk to develop infection caused by *Stomatococcus mucilaginosus* [19]. Another gram positive bacteria such as *Listeria- monocytogenes* and *Rhodococcus equiar* are frequently isolated from immunocompromised patients [20].

The morbidity and mortality associated with gram negative bacteria is increasing except methicillin resistant *Staphylococcus aureus* (MRSA) and vancomycin resistant *Enterococcus* (VRE) in neutropenic cancer patients. Among gram negative bacteria *E. coli* and *Klebsiella pneumoniae* were accounted collectively about 60-65% in neutropenic cancer patients. Apart from other enterobacteriaceae, *Pseudomonas aeruginosa* and *Acinetobactor* species are also

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isolated among patients [23] Uncommon pathogens including *Capnocytophaga, Stomatococcus mucilaginous, Bacillus cereus, Leuconostoc spp., Corynebacterium jeikeium, Rhodococcus spp., Moraxella catarrhalis and Burkholderia cepacia* are also isolated from neutropenic cancer patients. Now these organisms are gradually increasing in among patients [24].

- **Polymicrobial growth:**

Polymicrobial infections are accounted for 15% in cancer patients. These infections are associated with pneumonia, cholangitis, bacteremia, neutropenic enterocolitis, perirectal infection and biliarly infection. The majority of infection caused by enteric gram negative bacilli, Enterococcus and Candida species and frequently isolated from abscesses and blood culture [25]. Norgaard et al reported 358 episodes of hematological malignancies and 14% of cases had Polymicrobial bacteremia. The ratio of gram negative and positive pathogens accounted for 60% and 14% in this setting [26].There is less and incomplete information regarding polymicrobial infection in neutropenic cancer patients. Most of studies focus on bloodstream infections caused by single organism and have no information about polymicrobial infections.

- **Changing pattern of infection in cancer patients:**

The international antimicrobial therapy cooperative group of European Organization for Research and Treatment of Cancer (EORTC) has been initiated clinical trials, laboratory research and antimicrobial treatment for neutropenic cancer patients since 1974. The data of these studies revealed that major changes have been witnessed in bacterial pathogens causing infections in among patients.16 In the 1970s, bacteremia caused by gram negative bacteria was reported 70% in febrile neutropenic cancer patients. By the mid of 1980s this situation had been completely changed, gram positive bacterial accounted for 70% of all

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infections among patients and only 30% of infection caused by gram negative bacteria [27-30]. The reason of increasing number of gram positive was bacteria due to the administration of aggressive chemotherapy and radiation therapy regimes that cause severe mucositis, prolonged use of indwelling catheters, wide spread use of prophylactic agents such as fluoroquinolones and empirical antibiotics treatment with activity against gram negative infections [31]. Gram negative bacteria are more sensitive to fluoroquinolones and third generation of cephalosporin than gram positive bacteria. Therefore, it plays an important role in developing Streptococcal bacteremia especially when these regimes are used with H2 blockers and antacids. Widespread use of fluoroquinolones is responsible for shifting the etiological pattern of bacteremia in neutropenic cancer patients [32]. In gram positive bacteria coagulase negative Staphylococcus replaced Staphylococcus aureus as the predominate organism, Escherichia coli and Klebsiella species remained the most commonly isolated as gram negative pathogens. Bacteremia due to Pseudomonas aeruginosa was decreased and Acinetobacter species and Stenotrophomonas maltophilia were gradually increased [33]. Increased rate of bacteremia (from 20-28%) in febrile neutropenic cancer patients is reported by European Organization for Research and Treatment of Cancer (EORTC) in its last trail (XIV).The reason of that changing trend in pathogens to increase in proportion of bacteremia caused by gram negative bacteria [37] Haupt et al pointed out that etiological pattern of pathogens that cause bacteremia in cancer patients is changing again. Study showed an increase of 3.4% per year in incidence of gram-negative bacteremia among children treated for solid tumors from 1985-1996 in a single institute [34].Two similar studies showed an increasingly rate of gram negative bacterial infection among patients with late-onset bacteremia followed by bone marrow transplantation [35-36].

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Table 1. Pathogenic bacteria isolated from neutropenic cancer patients

Common gram positive bacteria
Staphylococcus aureus
Coagulase negative Staphylococcus
Streptococcus pyogenes
Streptococcus viridans
Enterococcus species
Corynebacterium species
Common gram negative bacteria
E.coli
Klebsiella species
Pseudomonas aeruginosa
Acinetobacter species
Uncommon isolates
Capnocytophaga
Stomatococcus mucilaginous,
Bacillus cereus,
Leuconostoc species
Corynebacterium jeikeium,
Rhodococcus species
Moraxella catarrhalis
Burkholderia cepacia

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- **Antimicrobial prophylaxis:**

Bacterial infections are the most serious complication in patients suffering from various types of malignancies. Patients are more susceptible to infection due to profound neutropenia during cytotoxic chemotherapy. These patients are required immediately broad spectrum empirical antimicrobial therapy. Before putting these patients on such therapy, it is essential to monitor locally prevalent pathogens, their susceptibility pattern and risk assessment. Talcott et al classified patients suffering from neutropenia into four groups on the basis of risk involvement. The patients who were already admitted in hospital considered as group first and out patients with underlying disease, without progressing infection assigned group second and fallen under low risk group. Group third included out patients whose underlying disease was uncontrolled and another group forth had fever, severe neutropenia and other medical complications. These patients were recognized under high-risk group [37-38]. The patients those classified under low-risk group require short (4-48 hours) hospitalization followed by out patients care or administrate home based antibiotics therapy. These patients need less intensive care and treat entire episode as out patients. On the other hand patient who considered under high risk category are more prone to serious infection and often admitted to hospital followed by treated with empirical intravenous antimicrobial therapy. These patients develop serious medical problems therefore it is essential to have close monitoring for response to therapy and drug toxicity to improve treatment outcomes.

The combination of antimicrobial agents such as penicillin or cephalosporin with an aminoglycoside is the best therapeutic approach to treatment of febrile neutropenic patients.[40] The advantages of this type of regimen including a potential synergic effect against gram negative bacilli and possible to reduce of emergence of resistant strains [39-41]. The combination an antipseudomal carboxypenicillin or ureidopenicillin, piperacillin with an aminoglycoside (gentamicin, amikacin, and torbramycin) is widely used and recommended

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regimens to treat high risk neutropenic patients. The success rate is ranging from 71-76% when an aminoglycosides is used with combination of extend-spectrum cephalosporin such as cefoperazone and ceftazidime [15, 32]. Combination regimes including two betalactamase (carbapenicillin and ticarcillin) with combination of cephalosporin has broad spectrum coverage against gram negative bacilli especially Klebsiella species, which were resistant to carboxypencillin. This regime is less toxic and success rate is equal to an aminoglycosides-based regimes.Prevalence and development of recurrent resistance is observed in gram positive pathogens in many centers due to poor efficacy of an aminoglycosides plus beta-lactamase containing regimes. Vancomycin with beta-lactamase has broad spectra against gram positive infections and convenient to administrate in neutropenic.

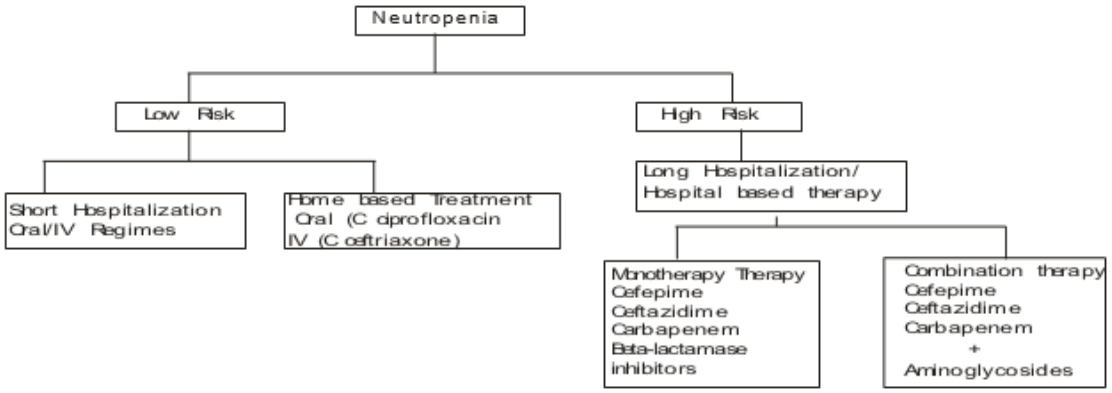

Figure 1. Risk assessment in neutropenic cancer patient

Cancer patients [28]. Monotherapy is associated with a trend towards better survival, a significant advantage in preventing treatment failure, fewer side effects and similar super infection rates [42-44]. Monotherapy is superior to conventional antibiotic combinations (piperacillin/cephalosporin third generation/aminoglycosides). Imipenem has lower side's

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effects and shorter period of fever, thus imipenem is an ideal antibiotic monotherapy in neutropenic cancer patients [9]. Imipenem was also more effective than two aminoglycoside-containing combination (ceftazidime plus amikacin and imipenem plus amikacin) in a study [15]. Use of oral antibiotic treatment in patients with febrile neutropenia is helpful to identify low risk patients. Different therapeutic options of oral antibiotic have been tried. It is commonly used in out patient's treatment to reduce resistant nosocomial infections. There are many studies on using fluoroquinolone as a prophylactic empirical regime in neutropenic cancer patients [5]. The data showed that oral use of ciprofloxacin, norfloxacin and enoxacin have reduced gram negative septicemia in such patients. Although extend spectrum of fluoroquinolone is effective and widely use for infection caused by gram positive bacteria but it is responsible for emergence of drug resistance [6].

2. Conclusion:

The monitoring of bacterial shift and locally prevalent pathogens and their susceptibility pattern must be observed to reduce the mortality in neutropenic cancer patients. Clinicians should adopt appropriate guidelines for the use of prophylactic and therapeutic antibiotics which would improve the outcome and prolonged survival in cancer patients with neutropenia.

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