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Study of Bacterial Pathogens and Viral Infections in Neutropenic Cancer Patients

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The increase use of intensive cytotoxic chemotherapy regimes achieve maximum antitumor activity, and cause of severe neutropenia. Neutropenic cancer patients are prone to infection when they become febrile. Bacterial infections are predominating among these patients. The bacterial infections in such patients are differ from institution to institution and is influenced by factors such a use of prophylactic antimicrobial agents. The treatment of neutropenic patients is possible by adoption of successful empirical antimicrobial therapy to eliminate the majority of bacterial pathogens.

Common sites of infection

The most common sites of infection in neutropenic patients are bloodstream (20-25%), respiratory tract (25-30%), urinary tract (10-15%) and gastrointestinal tract (5-10%). Skin infection accounted for 10-15% and other sites including meanings, bones and joint infections (1-5%).[61]

Common Bacterial pathogens

Rolston and Wisplinghoff pointed out that gram positive pathogens are commonly isolated in neutropenic cancer patients. The coagulase negative *Staphylococcus* is the predominant pathogen followed by *Staphylococcus aureus, Enterococcus* species and viridance group of *Streptococci.* Colonizing of bacteria on skin may also cause of infection, it includes catheter related bacteremia. *Corynebacterium* species and bacillus species were frequently, isolated from these devices [62, 63]. *Listeria monocytogenes* and *Rhodococcus equi* are also encountered in neutropenic patients. *Streptococcus* species including *Streptococcus pneumoniae* and beta hemolytic *Streptococci* are also important pathogens[64, 65].

In gram negative bacteria *E. coli* and *Klebsiella pneumoniae* were accounted collectively about 60-65% in neutropenic cancer patients. Apart from other enterobactereace, *Acinetobactor* species is also isolated among patients.[66] Uncommon pathogens are also identified such as *Capnocytophaga, Stomatococcus mucilaginous,*

Bacillus cereus, Leuconostoc spp., Corynebacterium jeikeium, Rhodococcus spp., Moraxella catarrhalis and *Burkholderia cepacia* are also isolated from neutropenic cancer patients. These organisms now gradually increased in neutropenic cancer patients.[72]

Changing trends in infection

In past two decades the major changes have been seen in bacteria causing infection in cancer patients. A shift from predominant of gram negative bacteria to gram positive bacteria has been observed. European Organization for Research and Treatment of Cancer (EORTC) is an international organization. The organization conducts large numbers of clinical trails on cancer patients including laboratory research in Europe. Randomized controlled trials conducted by this organization reflected changing pattern of infection in cancer patients. The incidence of bacteria in cancer patients has changed considerably over past four decades[3].

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 infections among patients and only 30% of infection caused by gram negative bacteria.[67, 82] The reason of increasing number of gram positive bacteria due to the administration of aggressive chemotherapy and radiation therapy regimes that cause severe mucosititis, prolonged use of indwelling catheters, wide spread use of prophylactic agents such as flouroquinalones and empirical antibiotics treatment with activity against gram negative infections.[69] 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 *Acinetobactor* species and *Stenotrophomonas maltophilia* were gradually increased.[70]

The changing trends in pathogens have been confirmed by the finding in the therapeutic procedures. More intensive treatment of cancer leads to more severe damage to mucosal barriers and increase risk of infection. The six years of study on bacteremia in febrile neutropenia was carried out by Aqunio *et al* (1995). They studied 153 episodes of bacteremia in pediatric cancer patients. In early three years gram positive (74%) organisms were frequently isolated and in later three years gram negative organisms were reported with increasingly and represent 50%. In gram positive bacteria *Staphylococcus epidermidis* and in gram negative *Pseudomonas aeruginosa* was most common isolate.[71]

Gram negative bacteria are more sensitive to flouroquinalones 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 H_2 blockers and antacids. Widespread use of flouroquinalones is responsible for shifting the etiological pattern of bacteremia in neutropenic cancer patients.[73]

Drug resistance has become an important problem for gram positive bacteria. The use of flouroquinalones as a prophylactic has been associated with emergence of

resistance.[74] Bacteremia due to anaerobic bacteria was diagnosed in only 5% of patients with febrile neutropenia and a percentage that remained unchanged over the past 30 years.[75]

Haupt *et al* (2001) 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.[76] Two similar studies showed an increasingly rate of gram negative bacterial infection among patients with late-onset bacteremia followed by bone marrow transplantation.[77-78]

Viral infections in neutropenic cancer patients

Viral infections are most common cause of morbidity in cancer patients especially to pediatric patients. Viruses are directly affect cell-mediated immune system, thus increase the risk of developing serious and life threatening infections.[113]

Respiratory viruses

Respiratory tract infections caused by viruses are most common in all ages and major cause of morbidity. Children are prone to upper respiratory tract infections[114]. The common symptoms of upper respiratory tract infections are common cold, coughing, rhinititis and sore throat.[115] Lower respiratory tract infection occurs in pediatric patients in first year of the age including pneumonia and bronchiolitis. Bronchiolitis caused by various viruses and has been detected in 90% of case.[116-117] It is very difficult to distinguish viral and bacterial pneumonia on the basis of clinical symptoms.[118] Whether causative agent is bacteria or virus, depends partly on age group studies. Viral infections are common in pre school age and bacterial infections occur in under the age of 6 months.[119]

Limited studies have been conducted on respiratory viral infections in cancer patients. A research conducted based on viral cultivation, electron microscopy and immunofluorescence technique were used to detect viruses in clinical specimens collected from children undergoing chemotherapy.[120] An another studies conducted in 1990s and 2000s which revealed respiratory viral infections were more frequently observed in children with cancer. In these studies different methods were used such as polymerase chain reaction, ELISA, and laboratory cultivation (Table 3). Results showed 9-44% of respiratory samples had viruses. The most common isolated virus was *Rhinovirus (RV)* followed by *Respiratory Syncytical virus (RSV) Human metapenumo virus (hmpv) Coronavirus (Cov)* and *Human boca virus (HBoV)* .[121-125]

Adenovirus is responsible for different types of syndromes in neutropenic patients. These include gastrointestinal infection with or without hepatitis, urinary tract infection, pulmonary infection and disseminated infection with various organs and have fatal outcome. In bone marrow transplant patient the rate of incidence of adenovirus varies from 4.9% to 20.9% and mortality rate was high as 60%.[126]

Parainfluenza virus considers the most important virus as a cause of respiratory tract infection. Children are severally affected *Parainfluenza virus* type 1, 2, 3,

causing 10% cases of community-acquired pneumonia. [129-130] Lujan *et al* (2001) analyzed 274 children those undergoing hematopoietic stem cell transplantation and *Parainfluenza* type 3 considered as a cause of espiratory tract infection in such patients after transplantation.[131] Infection with influenza virus in adult hematopoetic stem cell transplant recipient was ruled out in many studies. Elting *et al* (1995) conducted a study on 294 episodes of influenza virus in adult patients suffering from leukemia. Authors concluded that influenza infections occurred through nasocomial route.[132]

The common complication of *Rhinovirus* in cancer patients are otitis media, common cold and sinusitis. In 1987, long *et al* reported that *Rhinovirus* is most common cause of respiratory tract infection in children suffering from hematological malignancies. Authors cultured *Rhinovirus* from 45 of 204 febrile episodes in cancer patients.[139] Similar study conducted by Arola *et al* (1995), they recovered *Rhinovirus* from 13 immunocompromised children, who all had an uneventful recovery.[121] *Rhinovirus* responsible for 25%, respiratory infection in adult bone marrow transplant recipient and was third most common viral agent after *Respiratory Syncytical virus* and *Parainfluenza virus*.[140] Ghosh *et al* (1999) identified *Rhinovirus* in 22 adult immunocompromised patients. Upper respiratory tract infection was found in majority, but pneumonia with a fatal outcome developed in 32% of case.[141]

Enteroviruses are mainly cause acute respiratory tract infection, aseptic meningitis and encephalitis. *Enterovirus* infection commonly occurred in neonates. Immunosuppressed patients are prone to *Enterovirus.* This virus can be recovered from respiratory secretions, cerebrospinal fluids, urine, stool and from solid tissues. *Enterovirus* has been reported as a causative agent of encephalitis, myocarditis and disseminated disease in pediatric haemopoietic stem cell transplant recepients. Five years of study on cancer patients conducted by Moschovi *et al* (2007). Results showed fatality rate was 15% due to *Entero*viruses.[142]

Herpes viruses remain major cause of morbidity and mortality in haemopoietic stem cell transplant recipients. *Herpes simplex virus* detected in 50% of oral swabs from children after induction of intensive chemotherapy. *Herpes* simplex pneumonia has been detected in pediatric patients with cancer.[143]

Fungal infection in neutropenic Cancer patients

Fungal infections are primary cause of morbidity and mortality in patients with malignancies.[145,146] Immunocompromised cancer patients are on high-risk by such types of infections. In general patients those suffering from leukemia and lymphoma and are neutropenic following high dose chemotherapy or bone marrow transplantation are severely affected by different fungal species. In past two decades opportunistic fungal infection has increased due to increased use of invasive medical devices and wide spread use of antibiotics.[147] *Candida* and *Aspergillus* species are predominant cause of fungemia in patient who suffering from hematological malignancies.[149]

Fungal infection is a serious complication in cancer patients. They require early diagnosis and antifungal treatment for prolonged survival. Isolation and identification

of fungal pathogen from blood sample is very difficult and takes one to several days. Laboratory diagnosis of fungal infections has been improved by development of DNA-based and serological techniques. These methods are more sensitive and has intensively evaluated as a diagnostic tool.[150] Candida species are normal inhabitant of oral cavity and gut. Invasion of Candida in bloodstream by colonization on injured mucosal surface after receiving intensive chemotherapy.

Fungal infection in cancer patients is a challenging health problem especially patients those undergoing myelosuppressive chemotherapy. Badice *at el* (2009) studied 209 patients with hematological malignancies. Blood samples were collected to evaluate candidemia by using PCR-ELISA method for the presence of the bands on ethidium bromide stained gel and hybridization with *Candida* species. Study reflected that twenty five (12.9%) patients had evidence of fungal infection in whole blood. Fungal species were further identified, and *Candida albicans* was the frequently isolated organism and encountered in 21 cases followed by *C. tropicalis* (3cases) and candidemia caused by *C. krusei* was diagnosed only in one case.[155] Pagano *et al* (2006) reported 538 cases of fungal infection in 18 different hematological units. Results reveled that over half (346/538) cases were caused by moulds, out of them 310 cases were caused by *Aspergillus* species, while infection caused by yeasts in 192 cases of them 175 belonged to Candida species.[148]

A surveillance study of invasive fungal infections in neutropenic cancer patients was studied by *European Organization for Research and Treatment of Cancer*. A total of 249 episodes of candidemia were reported in 245 patients. Monomicrobial growth observed in 233 episodes (89%), while 7 episodes (3%) were showed polymicrobial growth with different fungal species.

The remaining 09 episodes (8%) had mixed growth both fungi and bacteria. *C. albicans* was predominant species again and accounted for 70% (63) of 90 patients suffering from solid tumors, 36%(58) of 159 patients those had hematological malignancies. Non albicans candidemia was observed in 12-14% of cases, caused by *C.glabrata, C.tropicalis, C. parapsilosis* and *C. krusei* .[156]

Candidemia was diagnosed in 210 patients out of 83 those suffering from cancer. Candidemia caused by *C. albicans* was accounted for 57.8%, followed *C. parapsilosis* (27.7*%), C.tropicalis* (13.3%), *C. galbrata* and *C. krusei* were infrequent (3.6% each). Results showed that candidemia caused by non *Candida albicans* species was reported in 78.9% of episodes in patients suffering from hematological malignancies and 51.6% in those patients who had solid tumors.[157]

Many changes have been observed in epidemiological shifting of candidemia in cancer patients. In 1990s candidemia caused by *C.albicans* was about 80-90%.[151] During the following ten years, the National Nasocomial Infection Surveillance system reported decline in *C.albicans* infections.[152]

Fridkin and Jarvis (1996) reported that candidemia caused by *C.albicans* has fallen to about 50%, while significant rate of increasing have been reported in the incidence of other *Candida* species.[153] A study was conducted under the project of Surveillance and Control of Pathogens of Epidemiologic Importance in mid of 1990s on epidemiological shifting in candidemia caused by *Candida* species. In this study a total of 934 cases of candidemia were diagnosed. About half (53.2%) of infections

caused by *C.albicans*, followed by non albicans species *C. galbrata* (20%), *C.tropicalis* (12%) ,*C.parasilosis* (10%), *C.krusei* (3%) and other species were accounted for (2%).[154]

Banerjee *et al* (1991) collected data between 1980-1990 from 124 different hospital of United State. The Project was carried out under National Nasocomial Infection Surveillance system. The hospitals were categorized as small non teaching hospitals (<200 beds), large non teaching hospitals (>200 beds), small teaching hospitals (<500 beds) and large teaching hospitals (>500 beds).

Incidence of bloodstream infection was increased in all hospitals ranging from 70 to 279%[160]. (Table 4)

Fungal infections are successfully controlled by administration of various antifungal agents such as amphotercin B, fluconazole, itraconazole, variconazole and caspofungin. Winston and his colleagues (1993) described that fluconazole is effective in eliminating colonization of *Candida krusei* in patients undergoing intensive chemotherapy for the treatment of hematological malignancies.[158] Anaissie *et al* (1996) pointed out that there is equal efficacy of fluconazole and amphotercin B in treatment of candidemia.

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