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Summary of Conference 4

INFECTIVE EVENTS DURING NEUTROPENIA AFTER THE EMPIRIC PHASE

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Usually an empiric antibiotic regimen in a given hospital is identical for all febrile patients, but such an approach may imply a suboptimal strategy, since it is probably not correct to consider febrile neutropenic patients as constituting a homogeneous population. Studies correlating the development of fever with subsequent documentation of infection in neutropenic patients have shown that approximately 20-30% of these episodes are due to bacteremias, 20% to clinically documented infections, 20% to nonbacteremic microbiologically documented infections, and the remaining 30-40% are possible or doubtful infections. Infectious death occurs in 21% of episodes with a focus of infection in comparison with 4% for episodes without a focus. Patients with a clinically proven focus of infection clearly represent a population different from patients with no clinically identifiable site. The most frequent skin and soft tissue infections are those which are associated with prosthetic devices involving mainly slime producing strains of coagulase-negative staphylococci. Mucositis, gingivitis and other dental related problems may occur in up to 85% of patients, featuring *Candida albicans*, viridans streptococci, enterococci or anaerobes. *Herpes simplex* virus may also play a role. Dysphagia or odynophagia may be due to chemotherapy or gastric reflux, but esophagitis is of infectious origin in the majority of cases, *Herpes simplex*, either alone or together with *Candida* species, being the most likely causative organisms. *Clostridium difficile* is the leading cause of antibiotic associated diarrhoea and colitis in patients who are exposed to prolonged or multiple courses of broad spectrum antibiotics. Management of the neutropenic patient with a new pulmonary infiltrate is complex, since as many as 40% of infiltrates may have a non-infectious etiology. Bacterial infections account for most of pulmonary infiltrates that appear as segmental shadows respecting the normal anatomical borders of the lung tissue. The majority of the focal infiltrates are caused by fungi in contrast to diffuse abnormalities which are usually not of direct bacterial or fungal origin. Next to adverse effects of cytotoxic therapy or irradiation, a number of causative microorganisms and pulmonary hemorrhage must be considered in case of a diffuse infiltrate. When a new infiltrate appears and progresses in patients who remain granulocytopenic, particularly in conjunction with fever and chest pain, a fungal pneumonia by *Aspergilus fumigatus* is the leading diagnostic consideration.

The infective events that occur early in the granulocytopenic period differ from the late infectious complications and the sequence of risk factors determines the order of infectious events considerably. Remission induction and consolidation therapy in acute leukemia, and conditioning regimens used to prepare patients for a bone marrow transplant both aim at maximal eradication of malignant cells. During the initial phase of profound granulocytopenia the initial implications are similar. This is illustrated by the clinical syndrome of oral mucositis, probably representing damage to the whole gastrointestinal tract. Bacteremia, mainly by streptococci that gain access to the blood stream through the disrupted mucosal barriers, local candidiasis and

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Herpes simplex virus infections predominate during the early phase of granulocytopenia. Since the inflammatory response in granulocytopenic patients is muted, the usual signs and symptoms of infection are characteristically absent. It is clear that on clinical ground alone it is virtually impossible to discriminate between patients with and without a bloodstream infection, unless symptoms compatible with sepsis are present. From the subgroup of patients with unexplained fever, more than 90% ultimately respond to antibacterial therapy, which suggests an occult bacterial origin of fever in many cases. Therefore it remains mandatory to administer broad-spectrum antibacterial agents without delay to all patients who become febrile during a chemotherapy induced episode of neutropenia. About one-third of episodes of bacteremia and candidemia occur during the first week of hospitalisation. After the first week the number of positive blood cultures gradually decreases and remains relatively constant after the fourth week.

In both the normal granulocytopenic patients and the bone marrow transplant recipient, the risk for second infections increases proportionally with the duration of granulocytopenia and includes resistant bacteria as well as non-bacterial pathogens. From day 10 onwards infections associated with central venous catheters will be encountered with a risk increasing with the length of time that the catheter is left in place, but during this phase the highest mortality is observed in patients with an infection of the lower respiratory tract, a finding which has been acknowledged in various studies. Whereas few patients develop invasive pulmonary aspergillosis early during the course of granulocytopenia, the danger of such an infection has become life-threatening reality when a patient becomes febrile after having been neutropenic for 20 or more days. The initial period of risk of bacterial and fungal infection resolves as the neutrophil count increases, but hepatosplenic candidiasis may become manifest in patients who recover from and episode of granulocytopenia. The infectious complications in bone marrow recipients are determined by the pace of reconstitution of the immune system. Acute graft-versus-host disease may induce ulceration of the gastrointestinal tract and abnormalities of granulocyte function as additional factors predisposing to infection. Treatment of acute graft-versus-host disease with immunosuppressive agents enhances the risk. Cytomegalovirus, adenovirus, fungi, and protozoa constitute the major pathogens after the period of initial engraftment.

The third major risk period begins approximately three month after transplant, at the time that chronic graft-versus-host disease develops. Sinopulmonary infections and cutaneous infecitons, probably related to the IgA deficiency and sicca syndrome are common. Varicella zoster is the most important cutaneous infection which occurs in 30 percent of all patients and in 45 percent of those with chronic graft-versus-host disease. Months, if not years after successful engraftment, encapsulated organisms like *Streptococcus pneumoniae, Haemophilus influenzae* type B, and meningococci have been shown to be responsible for rapidly fatal bacteremias and severe respiratory infections, attributable to the inability to make opsonizing antibody.