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Perspectives in Cancer Research

Prevention of Infection among Patients with Cancer*

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INTRODUCTION

CANCER patients are achieving an unprecedented higher rate of remission and remission duration from several malignancies but do so frequently with a preceding course of profound treatment-induced immunosuppression and granulocytopenia, which render them susceptible to multiple infectious pathogens. A strategy for the prevention of these infections will be presented to assist in the optimal and effective management of these compromised hosts.

TYPES OF ALTERED HOST DEFENSE

Rational infection prevention in cancer patients is predicated upon an understanding of those dysfunctions which alter host defense: granulocytopenia, impaired cell-mediated immunity, defective humoral immune response, breach of anatomic barriers and luminal obstruction. While any one or a combination of these defects in host defences may prevail in the cancer patient, one of the most common and life-threatening defects is granulocytopenia.

Granulocytopenia

The frequency of infection is inversely related to the granulocyte count, becoming notable when it is less than 500/μl with a precipitous rise in the episodes of infection in patients with granulocyte counts that are less than 100/μl [1, 2]. Factors other than the total number of granulocytes are operative in the granulocytopenic conditions, including the rate of decline of the granulocyte count. Patients with a rapidly declining granulocyte count are at higher risk of severe infection than are those with chronic neutropenic states, such as in chronic aplastic anemia, cyclic neutropenia or idiopathic neutropenia [3]. Protracted duration (10 days) of profound granulocytopenia (100/μl) is another important factor predisposing to severe infection, especially in those patients with acute leukemia, lymphomas, certain solid tumors or those receiving bone marrow transplantation. The latter condition usually entails approximately 3 weeks of severe granulocytopenia, as may induction therapy of acute non-lymphocytic leukemia.

Conditions of treatment-induced profound granulocytopenia usually produce concomitant loss of epithelial cell integrity. Altered mucosal integrity along the alimentary tract allows organisms to enter the blood stream or lymphatics. Loss of mucociliary clearance in the respiratory tract leads to retained secretions with aspirated organisms from the oropharynx. Cutaneous breakdown and exfoliation of the skin may occur. Skin damage may also be due to axillary shaving or procedures such as bone marrow aspirates, venipunctures and finger sticks.

Although the medical literature abounds with reports of virtually any organism complicating granulocytopenic patients, most infections are caused by a limited set of pathogens. The Gram-negative aerobic bacilli, *Escherichia coli, Klebsiella pneumoniae* and *Pseudomonas aeruginosa*,

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and the Gram-positive cocci, including *Staphylococcus aureus* and *S. epidermidis*, cause approximately three-fourths of all infections in granulocytopenic patients. As a complication of antimicrobial therapy for bacterial infections in patients with prolonged severe granulocytopenia, fungal infections due to *Candida albicans, C. tropicalis, Torulopsis glabrata* and *Aspergillus* spp. not uncommonly emerge. Infections are also limited in most cases to specific sites, the most common infections being pneumonia, oropharyngitis, oral mucositis, periodontal disease, esophagitis, periano-rectal lesions and cutaneous infection.

Impaired cell-mediated immunity

Certain cancer patients have an intrinsic defect in cell-mediated immunity, such as that which occurs in Hodgkin's disease [4], or they may acquire the defect through chemotherapy irradiation or malnutrition. Organisms which are most commonly associated with defects in cell-mediated immunity include *M. tuberculosis*, atypical mycobacteria, *Listeria monocytogenes, Nocardia asteroides* and non-typhi *Salmonella* species, certain fungi including *Cryptococcus neoformans*, as well as reactivated *Histoplasma capsulatum* and *Coccidioides immitis*, the protozoans *Pneumocystis carinii* and *Toxoplasma gondii*, the viruses Varicella zoster, Herpes simplex, and cytomegalovirus, and the helminth *Strongyloides stercoralis*. Nevertheless, these organisms remain relatively uncommon as pathogens compared to the more ubiquitous and previously mentioned aerobic Gram-negative bacilli and Gram-positive cocci, even in susceptible patients with altered cell-mediated immunity [5].

Impaired humoral immune response

Patients with hypogammaglobulinemia or with multiple myeloma are especially susceptible to infection due to the encapsulated pathogens *Streptococcus pneumoniae* and *Haemophilus influenzae*, due to the insufficient or abnormal production of opsonizing immunoglobulin.

Breach of anatomic barriers

This common problem is frequently associated with granulocytopenic patients and occurs in three settings. The first occurs as dysfunction of epithelial cells, as in enteric mucosal injury due to chemotherapy, or mucociliary dysfunction in the respiratory tract leading to retained secretions, and atelectasis with pneumonia or with cutaneous breakdown. The second setting occurs with iatrogenic insertion of such instruments as venous catheters, arterial lines, urethral catheters, endotracheal tubes and endoscopes. The third situation is the loss of normal physiologic control over certain barriers such as that which occurs with aspiration pneumonia in the obtunded patient or in urethral sphincter dysfunction due to spinal cord compression from an impinging tumor mass or as a consequence of primary or secondary brain tumor.

Luminal obstruction

Tumor may also impinge on the lumens of natural passages such as those of the urinary tract by prostatic, cervical or rectal carcinoma or of the bronchus by bronchogenic carcinoma. Other examples include obstruction of the common bile duct by pancreatic adenocarcinoma leading to ascending cholangitis and obstruction of the eustachian tube by nasopharyngeal carcinoma or by lymphomatous adenoidal tissue. The common mechanism occurring is the obstruction and stasis of a body fluid with subsequent overgrowth and infection by normal flora.

SOURCES OF INFECTING ORGANISMS

Endogenous sources

Weekly or twice-weekly surveillance culturing of nose, gingivae, axillae and rectum in hospitalized patients with acute leukemia demonstrated that more than 80% of infections are caused by organisms colonized at or near the infected site [6]; many of these pathogens are nosocomially acquired. A case in point would be that of a *Pseudomonas aeruginosa* pneumonia preceded by gingival cultures demonstrating the infecting organism. Another example is perianal cellulitis and bacteremia due to *Klebsiella pneumoniae* in a patient whose rectal surveillance cultures earlier grew this same organism.

Serial surveillance culturing is an intrinsic part of prevention and treatment of the neutropenic cancer patient. It provides ongoing data on efficacy of prophylactic measures by demonstrating whether common potential pathogens mentioned previously have been eradicated from the patient and whether these pathogens have developed resistance to antimicrobial therapy, thereby allowing their persistence. Surveillance culture data also allows selection of empiric antibiotic therapy to be directed at those potential pathogens already colonizing the patient. Such data define the degree to which patients acquire colonizing organisms from the hospital environment as part of their endogenous flora. Finally, results of surveillance cultures may indicate patient compliance with oral medications.

Changes in the normal oropharyngeal flora occur via altered binding of organisms to epithelial cell lectins in the oropharynx and other

mucosal surfaces due to the underlying disease and by alteration of the normal microflora by antibiotics and cancer chemotherapeutic agents [7–10]. Other factors that alter the normal microbial flora include invasive procedures such as placement of intravenous or urinary catheters, which provide a conduit for organisms normally excluded from these sites.

'Colonization resistance' is a concept developed by van der Waaij and his colleagues [11] which states that anaerobic flora of the alimentary tract contribute to deterring prolonged colonization of acquired organisms. For example, normal mice are colonized only after ingestion of 10^9 organisms, whereas gnotobiotic mice devoid of any alimentary tract flora are colonized by a much lower threshold of $0.5–1 \times 10^2$ organisms. This resistance to colonization by acquired organisms is dependent in part on the preservation of the native anaerobic flora of the alimentary tract [11, 12]. Eradication of the normal anaerobic flora in cancer patients can lead to loss of colonization resistance, the overgrowth of a hospital-acquired organism and the development of localized mucosal infection from which bacteremia may emerge due to frequently associated granulocytopenia with impaired ability to control local infection.

Exogenous sources

The most important source of exogenously acquired bacteria by the cancer patient is probably food. Aerobic Gram-negative bacilli derived from soil commonly colonize fruits and fresh vegetables. A typical chicken salad, for example, may contain *P. aeruginosa, K. oxytoca, P. mirabilis, P. fluorescens* and *E. agglomerans*. Yet virtually any food substance not properly cooked may serve as a source of potential pathogens [13]. Flowers, their vases or containers [14], faucet aerators [15] and ice machines [16] are potential sources for pathogenic Gram-negative aerobes.

Organisms may be transmitted in the air from man's respiratory tract and a diverse variety of environmental sources, such as nebulizers and humidifiers [17], fireproofing materials in hospital ceilings [18] and air-conditioning systems [19]. An airborne route of transmission also has been implicated by clustering of cases of *Pneumocystis carinii* in cancer patients [20].

Since Semmelweis's observations in 1847, the transmission of infection by physician's hands and its prevention by careful hand-washing remains an important principle of infection control. Other sources of organisms exogenously transmitted to cancer patients have been endoscopes inadequately decontaminated from previous patients [21], liquid soaps and cationic detergent disinfectants [22]. Transfused blood products may be occasionally contaminated with bacteria or may contain donor-derived organisms such as hepatitis B, non-A, non-B hepatitis, cytomegalovirus and *Toxoplasma gondii*. There is increasing evidence that the presumed agent(s) of the acquired immunodeficiency syndrome (AIDS) may be transmitted by transfusion of blood products [23, 24]. While a recent study [25] indicates that people rather than the environment are the major source of transmission of organisms to patients, appropriate measures to prevent transmission of potential pathogens to the neutropenic patient from the environment are also necessary.

Latent infection

Exogenously acquired organisms such as cytomegalovirus, Herpes simplex, Herpes zoster and *Pneumocystis carinii* may remain latent for years until the host becomes immunosuppressed. During the course of altered immune host defenses, especially that of T cell activity, these organisms may become manifest as active infections. Accordingly, antimicrobial prophylactic measures have been successfully developed against reactivation herpetic infections [26] and pneumocystis pneumonia [27]. Nevertheless, a most common problem confronting the practising oncologist is prevention of bacterial infection in granulocytopenic patients.

INFECTION PREVENTION IN GRANULOCYTOPENIA

Laminar air-flow rooms

Total protective isolation provides an environment in which the patient's endogenous flora is suppressed and the acquisition of new organisms is markedly reduced. The system requires a laminar air-flow room in which air is forced in a laminar unidirectional pattern from one wall through high-efficiency particulate air (HEPA) filters located in the opposite wall. Such filters remove particles greater than 0.3 μm in diameter thereby eliminating bacteria, fungi and some larger viruses [28]. This laminar air movement may also prevent accumulation of organisms shed by the patient in this environment. All items carried into the room must be sterile or nearly so. Food and water should have low bacterial and fungal counts. Sterile gloves, gown, cap, mask and shoe covers must be worn by personnel or visitors entering the room. A meticulous housekeeping protocol must also be followed. Although there are few studies evaluating the efficacy of laminar air flow without concomitant antimicrobial suppression of endogenous flora, certain data suggest that the acquisition of

potentially pathogenic organisms is decreased and that development of new infection is reduced by as much as 50% in patients within a laminar air-flow environment compared with randomized control groups [29, 30].

Oral non-absorbable antibiotics

Since the patient's endogenous microflora of the alimentary tract comprise the principal source of infectious organisms in the cancer patient, measures to prevent infection have included the complete suppression of all organisms in the alimentary tract or selective eradication of aerobic Gram-negative rods with persistence of colonization resistance by preservation of anaerobic organisms. An antifungal agent is usually administered with the antibacterial antibiotics.

Combinations of oral non-absorbable antibiotics have been gentamicin, vancomycin and nystatin (GVN), framycetin, colymycin and nystatin (FRACON), or neomycin, polymyxin, paromycin and nystatin. Amphotericin B at times has been substituted for nystatin in these regimens. These regimens have often been administered in conjunction with combinations of topical skin disinfection, orificial antimicrobial ointments, low microbial diets and total protected isolation.

Prospective randomized studies evaluating the efficacy of oral non-absorbable antibiotics have shown conflicting results [29, 31–33]. The variability of results in such studies is influenced by several factors. First, the frequent non-compliance with the oral medications may be followed by rebound overgrowth of potential pathogens and emergence of aminoglycoside-resistant organisms in the host flora [31, 34, 35]. Secondly, among the different chemotherapeutic agents and doses used, some such as the large single-dose regimen of daunorubicin used by Schimpff *et al.* [31] created more mucositis and more sustained profound granulocytopenia, in contrast to patients of Levine *et al.* [33], whose chemotherapy-induced granulocytopenia was shorter in duration. Thirdly, the use of liquid antibiotics instead of capsules or tablets may provide better prophylaxis against infectious oropharyngitis and esophagitis. Finally, a program of oral and dental hygiene as part of the protocol to reduce alimentary tract flora may also influence the observed infection rate in various studies of oral non-absorbable antibiotics [36]. In our opinion, comparative analysis of the available data indicate that liquid oral non-absorbable antibiotics effectively reduce the infection rate if the patient is at maximum risk of infection with an anticipated duration of profound granulocytopenia (less than 100/μl) of longer than 2 weeks, is compliant with the medication schedule and is managed in a total protected environment [37, 38].

Combined laminar air-flow room and oral non-absorbable antibiotics

That the combination of laminar air-flow room and oral non-absorbable antibiotics substantially reduces the frequency of new infections in profoundly granulocytopenic patients has been shown in various prospective randomly controlled studies in which the control group received neither prophylactic modality [29, 30, 31, 34, 39, 40]. However, the current daily patient cost for the combination of laminar air-flow room and oral non-absorbable antibiotics is approximately $1200, with an average length of isolation for most patients ranging from 30 to 50 days [41].

Furthermore, the combined modalities have not appeared to significantly improve the frequency of complete remission in acute leukemia [42] and have not influenced the rate of engraftment, interstitial pneumonitis or graft-versus-host disease in bone marrow transplantation [39]. However, Bodey *et al.* [43, 44] have demonstrated that a protected environment–prophylactic antibiotic program not only decreased the infection rate but also allowed higher doses of chemotherapeutic agents, thereby achieving a higher complete remission rate and lower fatality rate in patients with malignant sarcomas [43] and attaining a significantly longer duration of remission and survival in non-Hodgkin's lymphoma patients who received higher doses [44]. Although the advantages of laminar air-flow room and oral non-absorbable antibiotics are evident, the cost–benefit aspects of this regimen would appear to militate against establishing new laminar air-flow rooms in non-research settings. Instead, further research is required to reduce the cost and complexity of complete reverse isolation and microbial suppression [45].

Selective microbial suppression with preservation of colonization resistance

Clinical evidence suggesting the importance of colonization resistance was seen in patients receiving trimethoprim-sulfamethoxazole for prophylaxis against *Pneumocystis carinii* [27]. These patients realized a significant reduction in bacterial infections. Sleijfer and his co-workers [46] reasoned that since oral non-absorbable antibiotic combinations such as gentamicin, vancomycin and nystatin (GVN) suppress colonization resistance, drugs such as trimethoprim-sulfamthoxazole, polymyxin E or nalidixic acid, which suppress or eliminate potentially pathogenic aerobic Gram-negative bacilli without altering colonization resistance provided by

anaerobic organisms, may be effective in the prevention of infection in granulocytopenic patients. Accordingly, they conducted a controlled prospective randomized trial in which the 53 granulocytopenic patients receiving nalidixic acid, trimethoprim-sulfamethoxazole, or polymyxin E and amphotericin B had 2 Gram-negative or yeast infections among two patients, whereas the granulocytopenic control group of 52 cases had 18 such infections among 12 patients. Nine patients in the control group died of an acquired infection, whereas none of those receiving selective decontamination of the digestive tract died. Gurwith *et al.* [47] found a significant reduction of bacteremia in adults with acute non-lymphocytic leukemia who were randomized to receive trimethoprim-sulfamethoxazole versus no prophylaxis. A study at the University of Maryland Cancer Center (UMCC) which compared trimethoprim-sulfamethoxazole plus nystatin with gentamicin plus nystatin found the two regimens to be comparable in preventing infections in acute leukemic patients [48]. A subsequent study [49] at the UMCC which compared trimethoprim-sulfamethoxazole to nalidixic acid noted the prolongation of neutropenia with trimethoprim-sulfamethoxazole and the emergence of resistance to trimethoprim-sulfamethoxazole and to nalidixic acid. Such resistance to trimethoprim-sulfamethozole has been associated with bacteremic episodes in patients with acute leukemia [50–52]. Moreover, while trimethoprim-sulfamethoxazole in granulocytopenic patients suppresses the Enterobacteriaceae and maintains the normal anaerobic flora, concurrent administration of parenteral antibiotics temporarily but markedly disrupts anaerobic flora and the colonization resistance which these organisms provide [53]. Other trials of trimethoprim-sulfamethoxazole for infection prophylaxis in patients with acute leukemia have shown conflicting results [51, 54].

Among the various factors which may account for the discrepancies in independent studies of selective microbial suppression an important factor is compliance. Pizzo *et al.* [55] randomized patients with acute leukemia, non-Hodgkin's lymphoma and solid tumors between the combination of trimethoprim-sulfamethoxazole with erythromycin and placebo for systemic prophylaxis against Gram-negative infections. There was no difference between the two groups in the frequency of fever or infection. However, when compliance, as measured by a scoring scale, was considered, a significant reduction in the frequency of fever and infection was observed in patients with excellent compliance. Moreover, patient compliance appeared to be both an important dependent and independent variable, since patients in the placebo group who also had excellent compliance achieved a significant reduction in the rate of fever or infection. A placebo-controlled trial conducted by Malarme *et al.* [56] of oral vancomycin plus gentamicin and trimethoprim-sulfamethoxazole in granulocytopenic cancer patients showed that although the combination of all three antibiotics was associated with no Gram-negative bacillary infections, the same combination was least tolerated by patients due to side-effects of nausea and diarrhea. This combination was discontinued in 49% of the cases, resulting in a lower mean and median duration of prophylaxis. While patient compliance may also be measuring attitude, hygiene and dietary habits, this factor is an important variable which should be considered in future trials of any oral antimicrobial prophylactic regimen.

The oral trimethoprim-sulfamethoxazole and nystatin combination is better tolerated, is less costly ($5 versus $150/day for oral non-absorbable antibiotics) and improves patient compliance compared to conventional non-absorbable regimens. The combination reduces the rate of infection and fever in neutropenic patients, but since its use is accompanied by the emergence of resistant organisms, appropriate surveillance cultures are mandatory while following such patients [52, 57].

Antifungal prophylaxis

Most of the previously discussed oral antimicrobial regimens included an antifungal agent, usually nystatin or amphotericin B. Whether such oral antifungal prophylaxis effectively prevents oral or deep visceral candidiasis is controversial [58–62]. Although *Candida* may be suppressed by oral administration of either agent in large quantities such as 1×10^6 units of nystatin suspension every 4 hr, fungal esophagitis or oropharyngitis may still prevail [58, 59]. Problems with both compliance and the brief duration of time in which the antifungal agent sustains contact with the mucosa allow the proliferation of *Candida*. Patients should be instructed to swish the antifungal agent for a full minute and not to drink water or beverage soon after ingesting nystatin in order to prolong contact with the oral and esophageal mucosa. Amphotericin B compounded in Orabase® and applied to the gingiva every 8 hr allows for the sustained and slow release of amphotericin B, resulting in salivary concentrations of the drug which well exceed the minimal inhibitory concentration for most *Candida* isolates [63]. The combined preparation is available (Squibb) in Europe but not in the

United States. Amphotericin B was mixed with methylcellulose for prolongation of mucosal contact during a period of time at the UMCC but with uncertain benefit. Long-lasting inhibiting concentrations of amphotericin B can be achieved in saliva with lozenges of the drug [64]. These investigators indicate that amphotericin B lozenges may be preferable due to the stickiness and somewhat unpleasant taste of Orabase®. Amphotericin B lozenges given 3–4 times per day after meals might be a potentially effective regimen for reducing the frequency of positive throat cultures with *Candida* in neutropenic patients [64]. Ketoconazole, which has broad antifungal activity and relatively low toxicity, had at least the same overall efficacy at 200 mg twice per day when compared to nystatin, 1 million units of liquid every 4 hr. However, while colonization with *Candida* species was reduced, colonization with *Torulopsis glabrata* increased in those patients receiving ketoconazole [65].

A review of 110 fungemias between 1974 and 1977 at the Memorial Sloan-Kettering Cancer Center in New York showed increasing incidence of *Candida tropicalis* fungemia each year [66]. Among granulocytopenic patients whose surveillance cultures show colonization with *Candida* species, those patients colonized with *C. tropicalis* compared with *C. albicans* have a significantly greater rate of disseminated infection [67]. Earlier initiation of systemic antifungal therapy may be warranted for febrile granulocytopenic patients whose surveillance cultures reveal *C. tropicalis*.

Infections due to those yeasts which are less prevalent than *Candida* and *Torulopsis*, such as cryptococcal meningitis [68], carry a high mortality and are probably not reduced in incidence by oral nystatin or amphotericin B.

Local control of potential pathogens

Skin decontamination. Granulocytopenic patients commonly develop cutaneous infections, usually due to involvement by *Staphylococcus aureus, S. epidermidis* or Gram-negative aerobes, at sites of integumentary injury. Special care should be exerted in preventing infection during and after procedures such as venipunctures, finger sticks and bone marrow aspirates until the wound is healed. Povidone-iodine, hexachlorophene, chlorhexidene or vigorous washing with regular soap removes most potential cutaneous pathogens. A complete daily shower or bed-bath using chlorhexidene and a shampoo with chlorhexidene 3 times per week is used currently at the UMCC. The axillary and perianal areas are frequent sites of cutaneous infection due to Gram-negative bacilli, *S. aureus* or *S. epidermidis*, which may be prevented by swabbing the areas with povidone-iodine twice daily during granulocytopenia [69]. The perianal region should also be swabbed with povidone-iodine after passage of each stool.

Nasal colonization. The nose is a common source of *S. aureus*, which may colonize and infect the skin. Although the nasal carriage state has been notoriously difficult to eradicate, a combination of rifampin and cloxacillin [70] or a more complex regimen consisting of a 5-day course of rifampin, trimethoprim-sulfamethoxazole, intranasal bacitracin and hexachlorophene baths [71] has been effective. Rifampin should never be used alone because of the rapid development of resistance by *S. aureus*. Rifampin, 600 mg once per day, and cloxacillin, 500 mg 4 times per day for 5 consecutive days, eradicated the nasal carriage state in 62% of ANLL patients at the UMCC, at least for the length of neutropenia associated with induction chemotherapy [72].

Nasal carriage of *Aspergillus flavus* or *A. fumigatus* in patients with acute non-lymphocytic leukemia frequently precedes invasive aspergillosis [73]. A combination of granulocytopenia, airborne transmission of spores and the eradication of normal nasal flora by broad-spectrum systemic antibiotics contribute to localized *Aspergillus* involvement. Perhaps consideration should be accorded to use of a prophylactic amphotericin B nasal spray in neutropenic patients whose nasal surveillance cultures show no bacteria.

Dental prophylaxis. Since periodontal infections are relatively common during granulocytopenia in adults, appropriate dental hygiene is warranted. The UMCC currently maintains a program of professional removal of plaque, repair of caries and extraction of teeth with periapical abscesses, while especially emphasizing a daily program of brushing and flossing [36].

INFECTION PREVENTION IN ALTERED CELL-MEDIATED IMMUNITY

Tuberculosis

Patients with a positive tuberculin skin test who are to be immunosuppressed should receive prophylactic isoniazid, 300 mg each day, regardless of age. Hepatic enzymes, of course, must be monitored closely. Since the tuberculin skin test in cancer patients is often non-reactive, one should consider administering daily prophylactic isoniazid if the chest radiograph shows evidence of previously active pulmonary tuberculosis or if there is a history of previously untreated tuberculosis or of close contact with a relative or friend with active tuberculosis.

Protozoal infections

Hughes *et al.* [74] demonstrated that the frequency of pneumocystis pneumonia was directly related to the intensity of immunosuppression, with the highest rate occurring in children with acute lymphocytic leukemia. Administration of trimethoprim-sulfamethoxazole (150–750 mg/m^2/day) successfully prevented the development of pneumocystis pneumonia in comparison to a 21% frequency in the placebo group [27]. This regimen may also be coincidentally prophylactic against another opportunistic protozoan, *Toxoplasma gondii.*

Herpes virus infections

Varicella zoster infections may occur in any cancer patient but are especially common in patients with Hodgkin's disease and in bone marrow transplant recipients. Herpes zoster frequently occurs within 6–12 months following radiotherapy, corresponding to maximally depressed cellular immunity [75]. Since those with the lowest levels of Varicella zoster antibody also have the highest susceptibility to the virus, perhaps such patients should receive prophylactic zoster immune globulin each month starting with their first course of radiotherapy and continuing for a year. Patients receiving immunosuppressive therapy who have never had Varicella should receive zoster immune globulin within 72 hr of exposure to a contact with Varicella or Herpes zoster. If the zoster immune globulin is unavailable, intravenous gammaglobulin may be administered in lieu of it.

Acyclovir (acycloguanosine) was recently shown to transiently prevent Herpes simplex infections in allogeneic bone marrow transplant recipients [26]. However, strains of Herpes simplex resistant to acycloguanosine have appeared [76]. Furthermore, cytomegalovirus, a major problem among bone marrow transplant recipients, does not respond to acyclovir or any other agent evaluated to date [77].

Helminthic infestation

Patients from tropical areas may carry *Strongyloides stercoralis* in their intestinal tract. Immunosuppression of such patients can induce disseminated infection with associated Gram-negative bacteremia [78]. Prophylactic thiabendazole to high-risk patients proven to have *Strongyloides* by sigmoidoscopy may prevent dissemination.

INFECTION PREVENTION IN ALTERED HUMORAL IMMUNITY

Active immunization

Multiple myeloma is classically associated with pneumococcal infection [79]. Such patients are unlikely to respond reliably to pneumococcal vaccine due to impaired antibody response to pneumococcal capsular polysaccharide. While the occurrence of the overwhelming pneumococcal sepsis syndrome in splenectomized patients with Hodgkin's disease is rare [80, 81], these patients are frequently given the polyvalent pneumococcal vaccine. Post-immunization antibody levels in splenectomized patients with Hodgkin's disease are significantly lower than those in normal controls and tend to increase in time from therapy for lymphoma [82, 83]. If the pneumococcal vaccine is administered before splenectomy and therapy, the antibody response may be more favorable. Since vaccinated patients with Hodgkin's disease have developed pneumococcal meningitis and bacteremia [82], a high index of suspicion must still be maintained for pneumococcal disease in this population. All patients should be instructed to seek medical attention immediately if they developed a sore throat, cough, fever, sinusitis or other evidence of infection and should empirically receive either ampicillin or cefamandole in order to cover *Hemophilus influenzae* as well as *Streptococcus pneumoniae* pending cultures if there is evidence to suggest an emerging infection. Provided that it is administered several days before or after chemotherapy, the influenza vaccine produces protective antibody levels in cancer patients [84]. Accordingly, influenza vaccine should be routinely administered to these patients, unless contraindications exist.

Passive immunization

While the 'J5 antisera', a passive form of immunization directed against the core glycoprotein of Enterobacteriaceae, appears very promising experimentally and clinically in preventing and treating potentially lethal Gram-negative bacteremia, clinical experience is too limited to recommend its general use [85–87].

AUGMENTATION OF SYSTEMIC HOST DEFENSES

Prophylactic granulocyte transfusions

The previously mentioned immunization techniques are designed to augment systemic host defenses in those cancer patients with humoral immune impairment. Similarly, the replacement of granulocytes in granulocytopenic patients should decrease the rate of infection. Indeed, some trials of daily prophylactic granulocyte transfusions have demonstrated a reduction in the frequency of septicemia [88, 89]. The total number of infections in a multicenter study, however, was not reduced [89]; this study also showed a high frequency of pulmonary infiltrates,

which were also associated with increased mortality, in those patients receiving granulocyte transfusions. Schiffer *et al.* [90] found an unacceptably high rate of transfusion reactions and alloimmunization in patients receiving granulocytes from random donors, indicating that prophylactic granulocyte transfusions must be performed with HLA-identical donors to prevent untoward reactions but hereby precluding the use of prophylactic granulocytes in most centers. Problems in the study by Clift *et al.* [88] included significant donor side-effects, including iron-deficiency anemia and the need for arteriovenous shunts. Thus prophylactic granulocyte transfusions cannot be routinely recommended for granulocytopenic patients except in specialized centers equipped to identify HLA-identical donors, as in the setting of bone marrow transplantation where the granulocyte donor was also the marrow donor.

Lithium carbonate

Although lithium carbonate may shorten the course of moderate granulocytopenia (100–500/μl), it does not influence the duration of profound neutropenia (100/μl) and does not significantly diminish the infection rate in cancer patients [91].

SUMMARY

Recognition of the alterations of host defense allows a rational approach to preventing associated infections. One of the most effective strategies for preventing infection in the granulocytopenic patient is the combined use of oral non-absorbable antibiotics, laminar air-flow room reverse isolation with strict housekeeping techniques, low microbial diet, sterile water, and topical antiseptics and antibiotics. The prohibitive cost, however, warrants that this system be restricted to research settings. The suppression of aerobic Gram-negative bacilli and fungi and the preservation of colonization resistance with such combinations as trimethoprim-sulfamethoxazole and nystatin show promise in preventing infection in the granulocytopenic patient. Prevention of infection in neutropenic patients also requires attention to simpler but very effective measures such as immunizations, antimicrobial prophylaxis against intracellular and non-bacterial pathogens in high-risk patients, limit-

Table 1. *Strategies for prevention of infection in cancer patients*

I. Augment host defenses
  A. Vaccines: influenza, pneumococcal, 'J5 antisera'
  B. Nutritional support
  C. Leukocyte transfusions (limited indications, see text)
  D. Complete remission of underlying disease
II. Avoid or limit invasive procedures
  A. Limit use of all in-dwelling vascular lines
  B. Limit use of urethral catheters
  C. Careful technique of venipuncture, fingerstick, bone marrow aspirate
  D. Specific indications for bronchoscopy or gastrointestinal endoscopy
III. Reduce acquisition of potential pathogens
  A. Simple but effective techniques:
    1. Careful handwashing by patient and personnel
    2. Low microbial diet
    3. Non-contaminated water and ice
    4. Proper housekeeping technique
  B. Complicated techniques:
    1. Laminar air-flow rooms (total reverse isolation)
IV. Suppress colonizing flora
  A. Total microbial suppression: oral nonabsorbable antibiotics; skin and hair decontamination
  B. Selective microbial suppression (preservation of colonization resistance):
    1. Trimethoprim-sulfamethoxazole
    2. Nalidixic acid } with nystatin or oral
    3. Polymyxin } amphotericin B
  C. Topical and orificial antibiotics
  D. Skin hygiene
    1. Clorhexidene bathing and shampoo
    2. Povidone-iodine axillary swabs
    3. Perianal care

ing invasive diagnostic and monitoring procedures, hand-washing by all personnel between visiting patients, oral hygiene, low microbial diets, axillary and perianal swabbing, and care with venipunctures and marrow aspirates. Finally, while the recommendations for prevention of infection are likely to continue to change with resulting improvement in patient care [92, 93], a tabulation summarizing current practices can be established based on our current knowledge (Table 1).

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