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Prophylaxis of Infection in Granulocytopenic Patients

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Most reviews of infectious complications in granulocytopenic patients stress the critical role of infection as a primary cause of death, and in influencing the outcome of therapy of the underlying disease. Aside from documented infections, fever almost invariably occurs in neutropenic patients when their functioning neutrophil count plunges below 500/mm^3 and this usually prompts the initiation of systemic antimicrobial therapy, in spite of the fact that the microbial cause of fever often remains undocumented.

In this review, I shall briefly document the efforts that have been expended toward the prophylaxis of infection in neutropenic subjects [1–4]. Each of the broad categories of intervention is listed in Table 1, along with those microorganisms that appear to be affected by such measures. The bulk of work in recent years has been primarily addressed to antimicrobial prophylaxis with or without isolation procedures. Nonetheless, it must be acknowledged that there have been some studies in the area of antifungal prophylaxis, active or passive immunization, chemoprophylaxis of fungal infection, and attempts to prevent viral infection with drugs, antiserum, and biologic response modifiers like interferon and transfer factor. Other well studied, but still controversial approaches involve the use of measures aimed at augmenting host defenses such as the transfusion of exogenous leukocytes. The recognition that patients with neoplastic diseases become colonized and subsequently infected by organisms that are present in the environment or commonly contaminate food has led to measures aimed at limiting the access of specific infecting microbes. More than 15 years ago "total protective isolation" facilities such as the "Life Island" with laminar airflow filtration were used to hospitalize the highly susceptible patients (on an experimental basis). While some evidence exists that these isolation facilities are effective, these units are too expensive and cumbersome for routine use. Laminar airflow units have been difficult to justify on a cost/efficacy basis and presently the sheer demands on nursing time have virtually precluded their widespread use outside the investigative setting.

In 1975, Schimpff and colleagues published a landmark study in which they compared isolation within the environment of the laminar airflow room with conventional ward care. The most important part of their study was the recognition that patients managed in a laminar airflow room were also given prophylactic oral nonabsorbable antimicrobials. Therefore, one of the control groups not only received routine ward care, but received the same prophylactic oral antimicrobial regimen of gentamicin, vancomycin, and nystatin given to patients in the isolation facility. A third arm of the study consisted of patients who received general ward care. Both in terms of infection rates and of survival, the patients who were managed on the open

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Table 1. Intervention against infection

Intervention	Against			
	Bacteria	Fungi	Viruses	Parasites
Environmental control	GNB	Aspergillus	Varicella zoster	
Antimicrobial prophylaxis	GNB ? G+C	*? Candida*	Herpes	PCP Toxo
Prophylactic antibody (active, passive)	? GNB ? Pneumococci		V/Z Hep CMV	
Prophylactic granulocytes	GNB		↑ CMV	
Biologic response modifiers			TF–V/Z IF	

GNB = gram-negative bacilli; G+C = gram-positive cocci; PCP = *Pneumocystis carinii*; Toxo = *Toxoplasma gondii*; V/Z = varicella zoster; Hep = hepatitis; CMV = cytomegalovirus; TF = transfer factor; IF = interferon

ward with prophylactic oral antimicrobials did almost as well as the patients managed in the laminar airflow rooms. This is consistent with the experience of a number of investigators. True airborne infection, even in the highly neutropenic patient, is rare. Perhaps the best accepted example is that of pulmonary aspergillosis. Other so-called true airborne pathogens, such as varicella zoster, tuberculosis, and perhaps the Legionnaire's bacillus are rather infrequently encountered in most cancer treatment centers. The expensive part of laminar airflow is the air filtration equipment and the requirement for supportive services for the patient in total isolation. Single-room isolation with antimicrobial prophylaxis seems to be a more cost-effective compromise.

Oral nonabsorbable antimicrobial suppression regimens (or as some investigators have called them, "total decontamination regiments") are quite expensive and may be poorly tolerated. Anyone who has ingested oral gentamicin and/or polymyxin B is immediately aware of the unpalatability of such prophylactic agents. The suggestion that trimethoprim/sulfamethoxazole might be an alternative prophylactic regimen came from the work of Hughes and associates. They found the routine use of co- trimoxazole prevented pneumocystis infections in leukemic children and resulted in a generalized reduction in all bacterial infections in this patient population (the notable exception was an increase in oral candidiasis). Soon thereafter, other investigators began exploring the routine prophylactic use of trimethoprim/sulfamethoxazole to prevent sepsis originating from the gastrointestinal tract. While the majority of published studies seem to suggest a beneficial role for trimethoprim/sulfamethoxazole in this setting, major reservations have also been expressed. First, both trimethoprim and sulfamethoxazole are not oral, nonabsorbable agents, but are systemically absorbed. The sulfonamide component may be quite sensitizing. Second, while some studies have demonstrated an overall reduction in infection rates, resistance to either agent may emerge. Third, folate antagonism may result in the prolongation of neutropenia in recipients of trimethoprim. Fourth, other side effects like gastrointestinal intolerance may develop. Fifth and perhaps most important, trimethoprim/sulfamethoxazole is inactive against *Pseudomonas aeruginosa* and these bacteria are a major cause of serious infection in neutropenic patients.

At present, there is considerable interest and enthusiasm about the potential prophylactic role of the new quinoline

agents. Several agents of this class have antipseudomonal, antistaphylococcal, and antienterococcal activity with minimal impact upon the anerobic gastrointestinal flora. These would appear to be most attractive properties for prophylactic use. Only well-executed clinical trials, however, will be able to demonstrate their advantages over other regimens. A central issue in whether they will truly prevent serious systemic infections, not just "mask" infection by making bacterial cultures negative.

For nonbacterial infections, there has been some progress in certain areas. There is no doubt that herpes simplex infections can be prevented by the use of a acyclovir. The protection, however, seems to last only for the duration of prophylaxis. Infection rates quickly rebound as soon as the medication is discontinued. Varicella zoster immunoglobin is thought to have a definite use in the prophylaxis of chickenpox in exposed juvenile patients. The use of immunoglobulins or vaccines for hepatitis may have an indication in some immunocompromised patients. As mentioned previously, the routine use of trimethoprim/sulfamethoxazole is effective in preventing *Pneumocystis carinii* pneumonia. Such regimens may also be effective in preventing nocardial and toxoplasmal infection, but definitive proof is not available from controlled studies.

Perhaps the greatest area of need for effective prophylactic measures is the field of fungal infections. Nystatin and amphotericin B have been available for many years; more recently, ketoconazole has been introduced as an oral prophylactic agent. There has been a paucity of real evidence that these measures actually reduce the incidence of systemic candidiasis.

In view of the likelihood that many pharmacologic agents will be used in an attempt to prevent infection, I would like to comment on the nature of study design. The desirable characteristics of a prophylactic antimicrobial study are summarized in Table 2. Relatively few published studies have incorporated the majority of these desirable features. One of the major problems that I perceive in the published literature is not only a lack of well-designed double-blind trials, but the failure to exclude from study any patient who has evidence of fever or infection at the point of entry into the study. Many trials fail to assess patient compliance and use objective end points for microbiologic documentation of infection. In the final analysis, we are interested in not only the reduction of infection, but evidence that the use of prophylactic agents reduces systemic antibiotic usage, shortens the duration of febrility or clinically suspected infection, and improves survival. We must be concerned that prophylaxis can mask infection and predispose to emergence of resistant organisms. It is possible that prophylaxis will result in an overall reduction in the incidence of infections, but those that do occur are more severe and possibly more resistant to antimicrobials. Therefore, effective prophylaxis could still result in the same costs,

Table 2. Desirable characteristics of prophylactic antimicrobial studies

Randomized, double-blind study designs
Inclusion of patients who are free of infection and fever at randomization
Objective measurement of patient compliance with the prophylactic regimen
Inclusion of large numbers of patients with similar diseases and at the same stage of disease
Uniform treatment of underlying diseases
Minimization or elimination of variables that could affect infection rates (e.g., protected environments and prophylactic granulocyte transfusions)
Comparison of regimens according to the onset of fever, the first documented infection, and the start of antimicrobial therapy
Adequate intervals for prophylactic regimens to have taken effect before the beginning of the observation period
Objective end points of microbiologically documented infection for analysis
Evaluation of complications, including side effects and emergence of resistance
Analysis to include survival of treatment and control groups by life-table analysis

measured in terms of hospital charges for prolonged hospitalization, to say nothing of infection morbidity.

Augmentation of host defenses as a prophylactic measure is theoretically a highly appealing approach. It does not risk selection for antibiotic resistance, nor will drug toxicity ensue. It does not place the patient at risk of the psychiatric complications of management within a laminar air flow unit. However appealing these approaches may be, their implementation has met with only limited success. Augmentation of host defenses through active immunization has led to only limited gains against organisms such as the pneumococci or *Pseudomonas aeruginosa.* While my personal feeling is that such approaches can do no harm, the real impact upon disease incidence has yet to be well demonstrated. In the case of *Pseudomonas* immunization, one vaccine that I have used has been quite toxic in itself. Routine use of exogenous immunoglobulins to prevent infection, particularly with some of the newer preparations that can be more easily delivered intravenously is attractive, but expensive. Convincing evidence of prophylactic efficacy in neutropenic subjects is not yet available.

Finally, we have been through a period during the last 10 years when there was considerable initial enthusiasm for the use of transfused granulocytes to prevent infection. While such approaches may result in a reduction of some infections, complication rates associated with granulocyte transfusions are high, including a large number of pulmonary infiltrates. Several studies have now shown that granulocyte transfusions predispose to cytomegalovirus infection in the previously seronegative patient. The routine use of prophylactic granulocytes cannot be justified based on our current perception of the high risk of complications, not only from the physical infusion of granulocytes, but from transfusion-associated viral infections.

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