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Empiric Antimicrobial Therapy in Cancer Patients *

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A. Introduction

The majority of fevers which occur in granulocytopenic cancer patients appear to have an infectious etiology [1]. The practice of initiating empiric antibiotic therapy when the granulocytopenic cancer patient becomes febrile is now well established and has markedly reduced the early morbidity and mortality of infections in these patients. Nonetheless, infections still remain the leading cause of death in neutropenic cancer patients, necessitating refinements in the diagnosis and management of the complications in high risk patients.

The impetus for empiric antibiotic therapy in febrile granulocytopenic patients was the early death due to untreated infection (particularly *Pseudomonas* septicemia) when the granulocytopenic patient became febrile. Indeed, during the late 1960s and early 1970s, 50% of patients with *Pseudomonas* bacteremia died within 72 hours of their initially positive blood culture [2]. The early initiation of antibiotics significantly reduced this early mortality. Nonetheless, a number of questions regarding the role of empiric antimicrobial therapy for cancer patients in the 1980s can still be asked, including: Who should receive empiric therapy and when should it be started? What constitutes appropriate initial empiric therapy? How should the initial therapy be modified for patients who remain graulocytopenic or who fail to respond to the initial regimen? How long should empiric antibiotics be continued?

In dealing with the first question, who should receive empiric therapy and when should it begin, it appears that granulocytopenia is probably the single most important risk factor for infection in cancer patients [3, 4]. Whether or not all granulocytopenic patients require prompt empiric antibiotic management when they become febrile (i.e., patients with solid tumors as well as patients with hematologic malignancies) has been addressed in a number of recent studies. In a survey of 1001 consecutive episodes of fever in 324 pediatric and young adult cancer patients at the NCI, Bethesda, Maryland, there was no apparent difference in the incidence, pattern, or severity of infectious complications that occurred, regardless of the patients' underlying malignancy, once they became granulocytopenic. There were comparable numbers of episodes of fever and granulocytopenia and of documented infections such as sepsis and pneumonia in patients with solid tumors as in those with hematologic malignancies [1]. Similarly, Markmann and Abeloff observed that in adults with solid tumors, early empiric antibiotics were useful in reducing infectious morbidity and mortality [5]. Thus, all granulocytopenic patients, regardless of their underlying cancer, should be considered to be at risk for infection and, once febrile, are candidates for early empiric therapy. The level of granulocytopenia that should prompt empiric ther-

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apy varies in different studies, with some recommending beginning antibiotics when the neutrophil count falls below 1000/mm³, while most would wait until the neutrophil count is less than 500/mm³. The rate at which the counts are falling may be as important as the absolute neutrophil number [6].

The degree of fever that should prompt therapy is defined differently at various centers. At the NCI, three oral temperatures above 38 °C or one oral temperature over 38.5 °C with a granulocyte count less than 500/mm³ is sufficient to begin empiric therapy. What is most important is for each center to adhere rigidly to predetermined criteria for defining high risk patients. This is particularly important since the diminished inflammatory capability of the granulocytopenic patient can mask the usual signs and symptoms of infection.

B. Preantibiotic Evaluation

Because untreated infections can be rapidly fatal, it is important that a thorough preantibiotic evaluation be carried out expeditiously. This should include a history and physical examination, at least two sets of preantibiotic blood cultures (if an indwelling line is present, peripheral vein cultures must also be obtained), chest X-ray, urinalysis, urine culture, and aspirate or biopsy cultures from accessible sites suggestive of infection. In spite of such an evaluation, it was not possible to differentiate patients with bacteremia from those with unexplained fever [1] in a recent prospective evaluation of 140 febrile granulocytopenic patients. More than half of the patients with bacteremia in this study lacked any specific physical findings.

C. Initial Empiric Antibiotic Combinations

Since approximately 85% of the initial pathogens are bacterial, the initial therapy is focused on bacterial pathogens. The original targets of empiric antibiotics were gram-negative bacteria, particularly *Pseudomonas aeruginosa,* and although gram-negative organisms still predominate, infections due to *Pseudomonas* have inexplicably declined. In contrast, infections due to gram-positive cocci (i.e., *Staphylococcus aureus* and *Staphylococcus epidermis*) have increased in recent years, in part due to the more widespread use of indwelling intravenous catheters [7, 8]. In order to give empiric cover for both gram-negative and gram-positive bacteria, broad-spectrum antibiotic therapy is essential. Thus, drug combinations are usually necessary and ideally should be bactericidal and synergistic, with a low potential for organ toxicity. In general, this has usually necessitated a combination of two or three antibiotics.

The importance of combination antibiotic therapy has been suggested since patients with gram-negative bacteremia have a greater than 80% survival when their isolate is sensitive to and treated with two antibiotics compared with a survival of 59% when the isolate is sensitive to only one of the two antibiotics [9–11]. In spite of the advantages of combined therapy, drug toxicity (particularly nephrotoxicity) is a concern in the cancer patient who is being exposed to many other toxic drugs.

The properties of some of the newer antibiotics raise the possibility of using them as single agents for the empiric management of febrile granulocytopenic patients. For example, in an ongoing study at the NCI, we are comparing monotherapy with ceftazidime (CTZ), a third generation cephalosporin, with our standard three-drug regimen of cephalothin (Keflin), gentamicin, and carbenicillin (KGC). To date, 349 episodes in 212 patients have been randomized to receive either combination therapy with KGC or monotherapy with CTZ when they became febrile and neutropenic (< 500 polys). The patients have been analyzed according to whether they had a documented infection or whether the etiology of their fever was unexplained. In addition, since the goal of empiric therapy is to protect the patient until results of the preantibiotic cultures are known, it is important to evaluate the efficacy of empiric antibiotic regimens both early in treatment – during the first 72 hours of therapy (i.e., prior to the time that the cause of the fever is

known), as well as for the entire duration of neutropenia. The success rate in the first 72 hours for both the CTZ- and KGC-treated patients with fevers of unknown origin (FUO) or documented infections was over 97%. In addition, the overall outcome (i.e., at the time of resolution of granulocytopenia) for patients with FUO was over 98% for both the KGC and CTZ arm, and was comparable for both antibiotic regimens for patients with documented infections. Thus, it would appear that with future advances in antitiotic development, it may be possible to provide effective initial empiric antibiotic management with a single antibiotic in the febrile neutropenic cancer patient. Continued study of this approach is, however, necessary.

D. Empiric Antifungal Therapy

A second problem is related to patients who remain neutropenic for extended periods and who may be at risk for second infections and superinfections, particularly due to fungi. Because even invasive fungal disease is so difficult to diagnose and because these infections are particularly difficult to treat, especially if the infection has already advanced at the time of diagnosis, an empiric approach to antifungal therapy has also been investigated in high risk patients. Currently, evidence for invasive fungal disease is present in 8%–69% of granulocytopenic patients dying with cancer [12–14].

Persistent fever is often the only indication of an early fungal infection. The major fungal organisms of concern in neutropenic patients are *Candida, Aspergillus,* Phycomycetes, and *Cryptococcus* [15]. Blood cultures are rarely of diagnostic help (being positive in fewer than 25% of cases of disseminated candidiasis and virtually never positive in aspergillosis or mucormycosis) [16].

It is notable that successful therapy of *Candida* and even *Aspergillus* has been accomplished when amphotericin B has been instituted very early in the course of the infection [17]. Thus, early empiric antifungal therapy has a rational basis for high risk patients. Several issues are relevant: Who are the patients at high risk? Which antifungal agent should be used? When should it be started and how long should it be continued?

Several studies suggest that patients who are persistently neutropenic and febrile in spite of a week or more of antibiotic therapy are at particular risk for developing a fungal infection. Burke et al. utilized empiric amphotericin B in acute leukemia patients experiencing recrudescent fever during empiric therapy with gentamicin and carbenicillin. The incidence of serious fungal infection was found to decrease from 33% to 10% when early empiric antifungal therapy was utilized [18].

In a study at NCI, we addressed the value of empiric antifungal therapy for patients with proven infections who remained febrile and granulocytopenic after 1 week of appropriate antibiotic therapy and who had alimentary tract colonization with *Candida.* Gastrointestinal colonization was associated with a heightened frequency of disseminated fungal invasion in the postmortem analysis by Young et al. Of the 329 episodes of proven infections we treated between November 1975 and December 1979, 22 (6.7%) had gastrointestinal colonization with fungi while febrile and neutropenic and had amphotericin B added empirically to their antibiotic schedule. It was notable that half of these patients actually defervesced within a median of 3 days after starting amphotericin B, despite remaining markedly granulocytopenic. Of the 22 patients, 20 began the amphotericin within 2 weeks after starting antibiotics and continued therapy until the resolution of granulocytopenia. All of these patients recovered, none with evidence of fungal infections [19].

A second study [19] prospectively addressed the issue of using empiric amphotericin B in the granulocytopenic patient with persistent unexplained fever. The question being addressed in this study was whether the persistent fever represented an undiagnosed bacterial infection for which the antibiotic regimen should be modified or whether it represented a secondary infection, perhaps due to fungi. The usual approach in the patient with persistent unexplained fever is either to discontinue anti-

biotics and reevaluate the patient or to continue the antibiotics in spite of the persistent febrile course. We compared these two approaches with one in which the antibiotics were continued and empiric antifungal therapy was added with amphotericin B.

Patients were randomized to one of three groups: I to have their broad spectrum antibiotics (Keflin, gentamicin, carbenicillin) discontinued after 7 days of therapy; II to continue antibiotics until resolution of fever and neutropenia; and III to continue antibiotics along with empiric amphotericin B until the resolution of fever and granulocytopenia. We observed that stopping antibiotics resulted in early complications, predominantly due to bacterial organisms, with 56% of the patients developing complications within a median of 3 days of stopping antibiotics. Continuing antibiotics seemed to prevent early bacterial infection, but 31% of the patients randomized to this group developed fungal infections. The patients randomized both to continue antibiotics and to receive empiric antifungal therapy appeared to do best in this study. While 1 of the 18 patients in this group did develop a fungal infection, this was with Petriellidium boydii, an organism resistant to amphotericin. Thus, it seems appropriate both to continue antibiotics and to give empiric amphotericin B in the persistently febrile granulocytopenic patient. We have chosen 7 days of persistent fever while the patient is on appropriate antibiotics as the criteria for initiating antifungal therapy, although this decision is somewhat arbitrary. Amphotericin B is the present drug of choice, although we are presently comparing empiric amphotericin B with high dose oral ketoconazole in patients who are persistently febrile and granulocytopenic after 1 week of antibiotics. If no evidence for a fungal infection is found, the empiric antifungal therapy can be discontinued when the patient's granulocyte count recovers. On the other hand, if a fungal infection is documented, a more extended course of therapy is indicated. The dose of amphotericin ranges from 500 mg for an uncomplicated fungemia to 2 g or more when there is evidence of organ involvement or a disseminated infection.

Antifungal therapy may also be administered empirically to patients with progressive mucositis and symptomatic esophagitis. Although other organisms, e.g., bacteria, herpes simplex, can cause symptoms of mucositis or esophagitis, patients with *Candida* lesions will generally improve within a 48 hour trial of empiric amphotericin.

E. Duration of Therapy

A third problem relates to the duration that empiric treatment with antibiotics and antifungals should be continued, particularly when the initial evaluation has not revealed a documented infection and yet the patient remains granulocytopenic for more than 1 week. In patients with a documented infection who have defervesced on therapy and who do not have a persistent site of infection, our practice has been to continue antibiotics for 10–14 days. The more difficult situation arises in patients who have no documented source of infection and who remain persistently granulocytopenic for over 1 week. Simply continuing empiric antibiotics in these patients without a source of infection must be balanced against superinfections and the risk for organ toxicity. A series of prospective trials at the NCI has addressed this problem by randomizing patients with a FUO either to discontinue their antibiotics or to continue them until the resolution of the granulocytopenia. The patients in these trials were stratified according to whether they had defervesced or remained febrile after the initiation of antibiotics. Within 3 days of discontinuing antibiotics, 41% of the FUO patients who had initially defervesced became febrile again and the organisms obtained on reevaluation were sensitive to the antibiotics they had previously received. Similarly, 56% of the FUO patients who had remained febrile in spite of antibiotics developed complications (including hypotension in 38%) within 3 days of stopping their therapy [20].

Although patients with persistent fever and granulocytopenia did best when empiric antibiotics were continued and empiric amphotericin was added, nearly half of these patients did well even when anti-

biotics were stopped. This has led some investigators to suggest that stopping antibiotics may be appropriate, providing the patient can be closely monitored and the antibiotics promptly reinstituted if necessary. However, because reliable end points for reinstituting therapy are vague and because these patients can deteriorate quite rapidly, it is our opinion that it is prudent to continue antibiotics, especially in the persistently febrile patient.

Other modifications of therapy may also be required in light of preantibiotic culture results and the patient's clinical response. Common modifications include the addition of vancomycin for *S. epidermidis* bacteremias and line site infections and the addition of clindamycin for anaerobic coverage in a patient with either perirectal tenderness, necrotizing gingivitis, or a possible abdominal source. The issue of narrowing the patient to pathogen-specific therapy versus continuing the broad spectrum therapy in patients who have microbiologically documented bacteremias and for whom the antibiotic sensitivities are known is also currently being addressed in a prospective randomized trial at the NCI. Thus far, no clear advantage has emerged to either strategem, but this study is ongoing.

F. Antiviral Therapy

In addition to antibiotics and antifungal drugs, antiviral agents have recently been added to the empiric therapeutic armamentarium. For example, acycloguanosine (Acyclovir) has been shown to reduce the incidence of herpes simplex stomatitis when administered prophylactically to patients undergoing bone marrow transplantation or to patients receiving intensive courses of chemotherapy [21]. Similar protection, however, has not been observed with other important viruses in the immunocompromised host, such as cytomegalovirus (CMV) although the recent observation that CMV pneumonitis may be prevented when patients receive passive immunization with high titer CMV antisera is intriguing [21–24].

G. Diffuse Pulmonary Infiltrates

Yet another situation in which empiric therapy may be advantageous is in the cancer patient with a diffuse interstitial pulmonary infiltrate. In the non-neutropenic cancer patient, the protozoan *Pneumocystis carinii* is a frequent etiologic agent, carrying a 100% mortality if untreated. Because of the nonspecific signs and symptoms, *P. carinii* pneumonia is virtually indistinguishable from other etiologic agents causing diffuse interstitial pulmonary infiltrates, including CMV, bacteria (e.g., *Legionella, Mycoplasma*), fungi (*Candida, Aspergillus, Cryptococcus*) and viruses (influenza, RSV, adenoviruses, rhinoviruses, and measles). Prior to the availability of trimethoprim–sulfamethoxazole (TMP/SMX), most clinicians agreed that biopsy confirmation of *P. carinii* was essential to justify the administration of potentially toxic treatment with pentamidine isothionate. Presently, there is considerable debate as to whether it is preferable to proceed directly to some invasive diagnostic procedure in the patient with a diffuse infiltrate or simply to begin antibiotics empirically and monitor the patient's response to this therapy [25, 26]. However, the appropriate "empiric therapy" can quickly become complicated and can include broad spectrum antibiotics and even antifungal agents in patients who are neutropenic and already on antibiotics when the infiltrate appears. The balance between the potential side effects of broad spectrum therapy and the risks of an invasive diagnostic procedure must be carefully weighed. Presently, at the NCI, we are addressing this issue in a study which randomizes patients with a diffuse interstitial pulmonary infiltrate to either appropriate initial empiric therapy or to an open-lung biopsy and pathogen-specific therapy. If the patient randomized to the empiric therapy arm does not stabilize or improve within 4 days, an open-lung biopsy is then performed as a further guide to therapy. The major question, of course, is whether an invasive procedure can be avoided. To date, 53 patients with diffuse pulmonary infiltrates have been evaluated and 29 have been eligible and randomized. 12 were randomized to immediate open-lung

biopsy, of whom 8 improved and 4 (33%) died and 17 to empiric therapy, of whom 15 improved and 2 (11.7%) died. Of the 15 patients who had an open-lung biopsy, 12 immediately and 3 after 4 days of therapy, 10 had *P. carinii* pneumonia, and 5 had nonspecific pneumonitis. Cutaneous T cell lymphoma and *Hemophilus influenzae* were diagnosed in addition to *P. carinii* pneumonia in two patients. Only one patient (with *H. influenzae*) had therapy changed as a result of the open-lung biopsy. Therefore, it appears that appropriate empiric therapy may also have a role in cancer patients with diffuse pulmonary infiltrates. Whether new procedures, such as pulmonary lavage, may provide an alternative diagnostic approach is presently being evaluated.

In conclusion, major advances have been made in decreasing the morbidity and mortality due to infectious complications in immunocompromised cancer patients with the use of empiric antimicrobial therapy, but refinements of management continue to be necessary. Clinical studies addressing these problems will be extremely helpful in defining appropriate empiric management of these patients.

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