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Dilemmas and Choices in Infection Management of the Cancer Patient

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Abstract—*Dilemmas related to fever and infection in the granulocytopenic cancer patient demand management choices frequently in the face of inadequate data to assure confidence in the decision taken. Key elements to decision-making include: recognition of the types of infections which tend to occur in these patients within one's own institution and the usual antimicrobial susceptibility patterns of the common pathogens within one's own institution. Second, one must differentiate the moderately granulocytopenic patient from one likely to have profound, persistent granulocytopenia and, hence, a high risk of mortality from gram-negative rod bacteremia. This information will assist in the selection of an initial empiric regimen. The same information in conjunction with the results of surveillance cultures and especially the results of repeat daily history and physical examination will assist in decisions related to discontinuation of the initial antibiotics, alterations in the original regimen, and decisions related to possible superinfections.*

INTRODUCTION

OVER THE LAST 20 years, there has been much intensive investigation of the approach to management of infections in patients with cancer, especially the patient who is granulocytopenic as a result of intensive cancer chemotherapy or in conjunction with bone marrow transplantation. During this time period, there has been a growing number of elegant, prospective, randomized, controlled trials of infection prevention and infection treatment approaches and numerous carefully conducted epidemiologic investigations which have helped to define the natural course of infection in these patients. Despite the vast array of information available, the individual physician is constantly faced with a series of dilemmas for which he or she must make a choice in patient management, a choice which may have a substantial effect on the patient's short term and long term survival. This article addresses some of those dilemmas and offers the author's current opinion as to approaching the decision-making process.

BACKGROUND

The incidence of infection in patients with granulocytopenia is directly correlated with the degree of granulocytopenia. Figure 1 demonstrates that the incidence of infection is particularly high when the granulocyte count is $<100/\mu l$ and especially notes that bacteremias are uncommon except in the patient who has essentially no circulating granulocytes [1]. This latter point has substantial implications for decision-making with regard to infection prevention and infection treatment. Although patients with any degree of granulocytopenia should be managed with basic hygienic measures such as handwashing, only the patients who will have profound, persistent granulocytopenia are at high risk for serious infection or bacteremia and, hence, only those patients should be subjected to the more intensive approaches toward infection prevention, such as the use of laminar air flow room reverse isolation, alimentary canal floral suppression, or both. Similarly, the patient who is profoundly granulocytopenic may well need to be approached differently with regard to empiric antibiotic therapy than the patient who has, say, between 100 and 1000 granulocytes/μl.

The first EORTC empiric antibiotic therapy study demonstrated that among 625 patients with granulocytopenia and the onset of new fever, at least 60% were infected and 22% had a bacteremia, about equally divided between gram-negative aerobic bacilli and gram-positive cocci [2]. The fourth EORTC trial which enrolled 1074 patients had 252 (23%) patients with a bacteremia with a slight preponderance toward gram-negative bacteremia (see the article in this issue by Glauser [23]) [3].

The organisms which caused the majority of these infections are the gram-negative aerobic bacilli, *Escherichia coli*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* and the gram-positive cocci, *Staphylococcus*

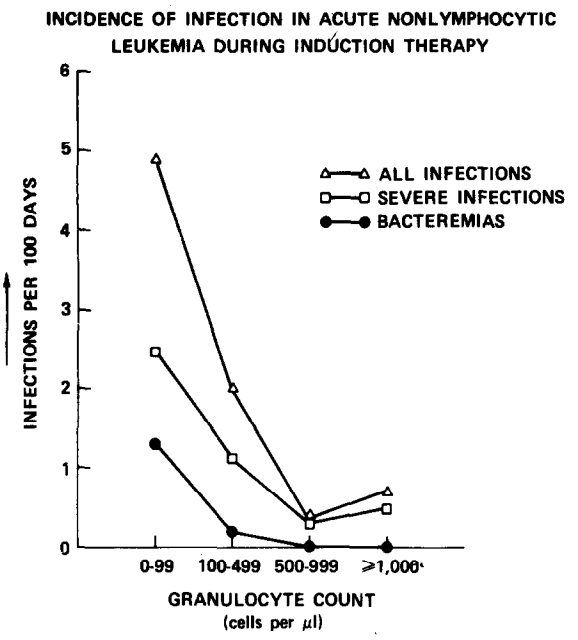

Fig. 1. Incidence of infection in acute nonlymphocytic leukemia during induction therapy. The incidence of infection rises as the absolute granulocyte count is reduced. Graph based on 64 newly diagnosed patients with acute nonlymphocytic leukemia treated with intensive chemotherapy at the University of Maryland Cancer Center between 1974 and 1977. Reprinted with permission from Mandell GL, Douglas R, Bennett JE, eds. Principles and Practice in Infectious Diseases, *3rd edn. Churchill Livingstone, New York, in press.*

aureus and *Staphylococcus epidermidis*. It is critical to recognize that each institution is different as to which organisms are more prominent and that within any institution, the rank order changes over time and may be quite different from area to area within the same hospital. For example, the University of Maryland Cancer Center used to find *Pseudomonas aeruginosa* to cause at least twice as many gram-negative rod bacteremias than any other single organism whereas, today, *Escherichia coli* and *Staphylococcus epidermidis* predominate. At the St. Jude Children's Research Hospital in Tennessee, gram-positive organisms not only predominate, but gram-negative bacteremia is rarely encountered [4]. Susceptibility patterns, likewise, vary from institution to institution, vary from location to location within an institution and vary over time. At our hospital, the susceptibility patterns for gram-negative bacilli within the Cancer Center are quite different from the susceptibility patterns of the same gram-negative rods when found in our Shock Trauma Center. In the mid-1970s, we had a very high incidence of gentamicin and tobramycin resistance among gram-negative rods necessitating the use of amikacin whereas today, for unclear reasons, gentamicin-resistance is uncommon. The fourth EORTC trial (again, see the article by Glauser [23]) was notable for a high degree of resistance among *Escherichia coli* to azlocillin, principally in a few of the European participating centers and not in the United States centers [3]. In the immediately preceding trial, azlocillin resistance at those same institutions was uncommon to *Escherichia coli*, the results with azlocillin plus amikacin were excellent, and, as a result, that regimen became the baseline for Trial IV [5].

This leads to a set of specific issues to consider when making a choice of regimen for initial empiric antibiotic therapy of the febrile neutropenic patient (Table 1). First, consider recent patterns of infection in the specific oncology unit where the patient is being treated; (2) consider the current institutional susceptibility patterns for the organisms which most frequently cause infection among oncology patients in the institution; and (3) consider the current susceptibility patterns for organisms causing infection within the oncology unit where the patient is being treated. Within this framework, it is then appropriate to take into account the results of published, prospective, randomized trials as an aid in guiding one toward rational treatment. At St. Jude Children's Research Hospital, vancomycin is included as part of the initial therapy and less attention is paid to concern for resistant gram-negative bacilli, because the patterns of infection suggest that such a course of action is most appropriate [4]. At the University of Maryland Cancer Center, however, gram-negative bacilli still represent substantive problems such that greatest initial attention is focused on them.

Within those parameters, one can consider either combination therapy or monotherapy. The most common approach remains a combination of a beta-lactam antibiotic plus an aminoglycoside. Most often, this is an anti-Pseudomonal penicillin plus an aminoglycoside but used almost as frequently is a third generation cephalosporin plus an aminoglycoside (Table 2). In recent years, once the fourth generation penicillins and the third generation cephalosporins became available, it became possible to combine one of each, a double beta-lactam combination, in a manner which gave two-drug coverage to the most prominent gram-negative organisms with modest gram-positive coverage. As will be noted below, vancomycin is part of a combination regimen particularly at those institutions with a high frequency of *Staphylococcus epidermidis* bacteremias. Monotherapy, usually with a third generation cephalosporin, such as ceftazidime, or the carbapenem, imipenem, has been found effective in a number of recent trials and is being increasingly utilized at this time.

Table 1. Initial empiric therapy of the febrile neutropenic patients. Consideration and choice of regimen

• Recent patterns of infection in the oncology unit.
• Current institutional susceptibility patterns for common organisms causing infection in the oncology unit.
• Current susceptibility patterns for commonly infecting organisms specific to the oncology unit.

Table 2. Empiric therapy of the febrile neutropenic patient

Cephalosporins	Penicillins	Carbapenems	Amingoglycosides	Vancomycin
Cefoperazone	Azlocillin	Imipenem	Amikacin	Vancomycin
Cefotaxime	Mezlocillin	plus cilastatin	Gentamicin	
Ceftazidime	Piperacillin		Netilmicin	
Moxalactam	Ticarcillin plus clavulanic acid		Tobramycin	

COMBINATION THERAPY VERSUS MONOTHERAPY

I am of the opinion that the patient who has profound, persistent granulocytopenia in an institution where the infecting organisms are frequently gram-negative aerobic bacilli would be best served by an empiric regimen composed of a combination of agents directed at these organisms. The rationale for the combination is discussed in detail by Glauser in the accompanying paper [23], but I would emphasize here the fact that the profoundly neutropenic patient is more likely to have a bacteremia and that the bacteremia is more likely to be caused by a gram-negative bacillus. Gram-negative bacteremia in these patients has a very high mortality. Unfortunately, many published studies which look at overall comparative results do not emphasize the results of this relatively small subgroup of patients. It is again worth noting that only about 10% of patients in the largest trials will have a gram-negative rod bacteremia and approximately one-half of these patients, or 5% of the total population of febrile neutropenic patients, will have a gram-negative rod bacteremia in the setting of profound, persistent granulocytopenia. As a result, the high mortality among these patients is not apparent in either trials with small numbers of patients or investigations of large numbers of patients which focus on overall group mortality rates. In the most recently published EORTC trial, Trial IV, as noted above, 1074 febrile neutropenic patients were entered onto study (Table 3). One hundred twenty-nine, or about 10%, had a single organism gram-negative rod bacteremia and, of these, only 53 had profound, persistent granulocytopenia. However, the overall response rates for beta-lactam–aminoglycoside combinations was only 23% (12 of 53) for these high risk patients compared to 82% (63 of 76) when the patient had more than 100 circulating granulocytes [3]. This point can be emphasized by an evaluation of 75 gram-negative rod bacteremias occurring in patients whose granulocyte count was $<100/\mu l$ during treatment at the University of Maryland Cancer Center (Table 4). Each patient received, promptly, an empiric antibiotic combination. Those with an aplastic bone marrow and, hence, persistence of their profound granulocytopenia had only a 29% response rate (12 of 41) compared to 85% (29 of 34) who had return of circulating granulocytes within a few days' time [6]. In retrospect, when antimicrobial susceptibility results returned, it was found that for patients with a recovering granulocyte count, it did not matter if the gram-negative rod was susceptible to both of the antibiotics or only one; in either event, about 85% of patients responded and survived. However, among those with persistent, profound granulocytopenia, only 7% (1 of 15 patients) responded when the organism was not susceptible to both antibiotics whereas 42% (11 of 26 patients) responded when the organism was doubly susceptible. Despite the much better response rate when the organism was susceptible to both antibiotics, the overall response rate of 42% (and note that most patients who did not respond to initial therapy succumbed to their infection) leaves much room for improvement in the future (Table 4). Incidentally, amongst those with persistent granulocytopenia in whom the organism was susceptible to both antibiotics, response rates were substantially better if the combination was synergistic or partially synergistic *in vitro* than when no *in vitro* synergism could be demonstrated [6].

Table 3. EORTC IV

Entries		1074
Exclusions		
Protocol violation	52	
Doubted infection	135	
Viral/fungal infection	15	
Evaluable episodes		872
Possible infection	342	
Clinically documented	225	
Microbiologically documented		
Without bacteremia	53	
With bacteremia	252	
Polymicrobial	33	
Single organism	219	
Gram-positive	90	
Gram-negative	129	129

Double beta-lactam combinations have proven to be especially useful in patients who have some degree of renal dysfunction or loss of auditory

Table 4. Seventy-five gram-negative rod bacteremias, initial granulocyte count <100/μl, response in granulocyte count

Overall response	Granulocyte count Remained <100/μl		Increased >100/μl
Improved/total	12/41 (29%)	$P = 0.0002$	29/34 (85%)
Pathogen susceptibility			
Two antibiotics	11/26 (42%)	$P = 0.004$	22/26 (85%)
Less than two antibiotics	1/15 (7%)		7/8 (88%)

de Jongh *et al. Am J Med* 1986, **80**, 96–100.

function. The studies completed to date all appear to be about equally efficacious to the beta-lactam–aminoglycoside combinations but have the advantage of no added nephrotoxicity or ototoxicity [7, 8]. Particularly for patients with acute leukemia who have multiple prolonged periods of granulocytopenia and, hence, multiple episodes of fever, double beta-lactams have proven to be especially useful to prevent the development of aminoglycoside-related deafness [9]. Although there had been initial concern for the development of resistance in the absence of the aminoglycoside, this concern has not been borne out.

Monotherapy, especially with ceftazidime or imipenem plus cilastatin, has been the subject of intensive investigation [10–12]. Without question, both of these agents used as monotherapy have been proven to be efficacious with little downside potential in the great majority of patients who were granulocytopenic and developed fever. However, it is not clear that the patient with profound, persistent granulocytopenia will have an adequate response rate to either of these monotherapy regimens. My recommendation therefore would be to consider monotherapy for the patient who is neutropenic but has >100 circulating granulocytes and in whom one can assume the granulocyte count will remain above 100/μl during the course of therapy. On the other hand, a combination would seem to be prudent for the patient with profound granulocytopenia or the patient who has a rapidly falling granulocyte count. As suggested previously, the specific choice of agent or agents should be dependent upon local patterns of infection and local patterns of susceptibility.

ADJUSTMENTS TO THE INITIAL EMPIRIC THERAPY DURING THE CLINICAL COURSE

Even more difficult than making a decision about the choice of an initial regimen are the dilemmas which one faces during the succeeding days. Among the decisions to be considered (Table 5) are:

Table 5. Issues to consider in altering initial empiric therapy

- Results of daily history and physical examination.
- Prior recent antibiotic therapy.
- Duration of granulocytopenia to date and into the future.
- Presence of vascular access device.
- Use of bone marrow transplant.
- Prior infections, especially viral or protozoan.
- Results of surveillance cultures.
- Recognition of recent institutional patterns.
- Duration of granulocytopenia to date and into the future.

Addition of vancomycin. Assuming vancomycin was not utilized in the initial regimen, it should be considered in either of the two following situations. First, the patient has signs and symptoms of infection at a site from which *S. epidermidis* or methicillin-resistant *S. aureus* are common. Exit site infections and tunnel infections associated with Hickman catheters are two such sites, but it is important to recall that most *S. epidermidis* infections arise along the alimentary canal from infections such as pharyngitis, esophagitis or colitis. If blood cultures or cultures from a specific site demonstrate *S. epidermidis* or methicillin-resistant *S. aureus*, then vancomycin is the agent of choice even if other drugs, such as cephalosporins, demonstrate efficacy *in vitro*. As a general rule, proven *S. epidermidis* infections should lead to the decision to either add or otherwise adjust therapy to include vancomycin. A second situation in which vancomycin might be added is the patient with persistence of fever after a few days of initial therapy in whom a definitive site of infection has not been documented and in whom surveillance cultures show a predominance of *S. epidermidis* at multiple locations such as pharynx and rectum or the patient has a Hickman or similar catheter in place and has clinical evidence which

suggests bacteremia despite negative blood cultures [13].

Alternative agents for gram-negative rods. Since the choice of initial therapy will have been based on general patterns of susceptibility for the institution and unit, then one would be inclined to change to other agents only if diagnostic cultures indicated a resistant organism or, in the absence of a microbiologically documented infection, a persistently febrile patient with an apparently deteriorating clinical course had surveillance cultures which demonstrated organisms resistant to the initial regimen [14].

Institution of granulocyte transfusions. There is excellent clinical evidence from prospective, randomized trials which indicate that granulocyte transfusions given daily on a prophylactic basis can prevent gram-negative bacteremia; however, there are multiple reasons, including technologic, toxic side-effects (pneumonitis, fever), alloimmunization (with consequent loss of ability to give platelets for thrombocytopenia), and induced infections (especially cytomegaloviral infection) which have discouraged further use of this technology. There is clinical evidence also that granulocyte transfusions given therapeutically can be effective, but the general feeling at this time is that the only patients for whom such transfusions are indicated are those with proven gram-negative rod bacteremia who are receiving appropriate combination therapy based on susceptibility assays yet are still failing to respond [15, 16]. Unfortunately, most patients who would potentially benefit from granulocyte transfusions are patients who have become alloimmunized due to frequent platelet transfusions in the past and hence will have no therapeutic effect from granulocyte transfusions.

Institution of antifungal therapy. As more and more patients are surviving for greater lengths of time and as cancer chemotherapy becomes more intensive, the frequency of fungal infections has substantially increased. From an approach of therapeutic nihilism of 15 years ago when amphotericin B was used very infrequently, today, based on the studies of Pizzo *et al.*, most oncologists will tend to give amphotericin B after about 5–7 days of continued fever [17]. The EORTC group studied patients who were persistently febrile and neutropenic; they were randomly allocated, beginning on day 4, to amphotericin B or not. With 58 and 51 such patients on study, there was a significantly greater frequency of defervescence but no difference in survival and no difference in the documentation of fungal infections (4 in each group or 7 and 8% respectively). Although this investigation, on the surface, failed to demonstrate an advantage for empiric amphotericin B, a subset of patients did clearly benefit. These were those patients in whom there was clinical evidence of infection without microbiologic proof. In other words, patients with fever but no other specific evidence of infection did not tend to benefit from the addition of amphotericin B on an empiric basis whereas those who had some clinical evidence of infection yet absence of microbiologic documentation did tend to benefit from amphotericin B [18]. I believe this is an important observation because it points out what we should all recall — not all patients who are febrile and neutropenic for a number of days are equivalent. The issue is to detect that subgroup of patients who are at greatest risk of having a fungal infection so that a potentially and frequently toxic drug can be given to those who may benefit while withholding it from the greatest number of patients for whom it is not required.

Addition of antiviral or antiprotozoan agents. The patient who is granulocytopenic, but does not have cellular immune deficiency, is generally thought of as not being at great risk of either protozoan or viral infections. Certainly, the patient who has been prepared and has received a bone marrow transplant is a patient who does have very severe cellular immune deficiency and, as noted in the accompanying paper by Meyers, has a very high frequency of developing herpes simplex virus, cytomegalovirus, varicella-zoster virus and *Pneumocystis carinii* infections [19]. What is less well recognized is that patients with leukemia who receive intensive cytotoxic chemotherapy also have a substantial number of herpes simplex and cytomegaloviral infections [20].

Concern for anaerobes or Clostridium difficile. It is an interesting observation that granulocytopenic patients rarely develop bacteremia with anaerobic bacteria. As a result, agents such as ceftazidime and aminoglycosides can be effective as empiric therapy even in their absence of activity against anaerobic bacteria. Indeed, since the anaerobic flora of the alimentary canal serves as a protective device (colonization resistance) to prevent newly acquired organisms from the environment from colonizing the alimentary canal epithelial cells, it may be advantageous to utilize antibiotics which do not have a tendency to suppress the intestinal and oral anaerobes [10, 21, 22]. One anaerobic infection which is becoming increasingly common, however, is that caused by *Clostridium difficile.* At many cancer centers, *C. difficile* is being detected in stool cultures with high and increasing frequency and, unfortunately, a substantial number of patients are developing moderate to severe signs and symptoms of toxin production. Rapid access to a toxin assay is therefore

important for these patients, and the presence of toxin should lead to the addition of oral vancomycin.

Length of therapy. There is considerable controversy as to the appropriate length of therapy in the febrile, neutropenic patient. Some general guidelines are as follows:

For the patient with a clinically or microbiologically documented bacterial infection, one should continue antibacterial therapy until fever and other signs and symptoms of infection have abated, usually 10–14 days. I personally see little sense in continuing broad spectrum antibacterial antibiotics for therapeutic reasons once the infection has been resolved. It has been recommended that the patient who continues to be granulocytopenic should have the antibiotic therapy continued until the granulocyte count recovers. I consider antibiotics given after the infection has resolved in this situation to represent 'prophylactic therapy' and would suggest that, if there is reason for prophylactic therapy, it should be labeled as such and probably agents other than those used as 'front line' therapy would be more appropriate. My own preference is to discontinue antibiotics when the infection has resolved, regardless of the granulocyte count, and if fever recurs or other signs and symptoms of infection develop, then one can, at that point, decide on the most appropriate course of action.

ISSUES TO CONSIDER WHEN ALTERING INITIAL THERAPY

The foregoing gave suggestions relative to specific issues which tend to arise during the course of a febrile episode in the neutropenic patients. There are a series of issues to consider when faced with the dilemma that the patient may not be responding adequately to the initial therapy and hence, an alteration in therapy may be appropriate (Table 5). Most important in making a decision are the results of daily history and physical examinations along with review of repeat chest X-rays and repeat cultures. The neutropenic patient has a poor inflammatory response, and, as a result, the history and examination on the first day or two may fail to reveal the site of infection whereas careful attention to repeat evaluation will most frequently lead one to the site of infection if an infection is present. Important in this regard is a repeat chest X-ray every few days, because only rarely does pneumonia manifest itself within the first 24 h among these patients. Prior antibiotic therapy will be a clue toward whether the patient might now be infected when an organism resistant to the more commonly used antibiotics or whether the patient may now have a fungal infection. Review of how long the patient has been granulocytopenic is pertinent because the patient may have had, during a prolonged episode of neutropenia, multiple courses of antibiotics which may have similarly altered the microbial flora. The presence of a vascular access device, such as a Hickman catheter, would lead one to be more concerned about a catheter-associated bacteremia, especially one caused by *S. epidermidis*. A patient who has received a bone marrow transplant, as noted above, has an additional spectrum of infections which may occur. Recognition that the patient may have had a prior viral infection, such as herpes simplex, will lead one to be more concerned about reactivation of the same virus during the current episode. Surveillance cultures can be of assistance in alerting the clinician to the presence of organisms resistant to the antibiotics being utilized (e.g. a beta-lactam-resistant *E. coli* or an aminoglycoside-resistant *P. aeruginosa*). Finally, and consistent with the approach to initial empiric antibiotic therapy, one needs to be cognizant of the types of infections and the organisms causing those infections within one's institution and, more specifically, within the unit where the current patient is undergoing therapy.

SUMMARY

The clinician faces a series of dilemmas in the management of fever and infection in the granulocytopenic patient. These dilemmas force one to make choices regarding therapeutic management, choices for which there is frequently inadequate data to generate a high level of confidence in the decision taken. However, one can face these dilemmas with a reasonable degree of assurance by first recognizing the types of infections which tend to occur in these patients within one's own institution along with knowledge of the antimicrobial susceptibility patterns not only within the institution but within that area of the institution where the patient is being treated. Armed with this information, the next stop is to determine the level of risk that the patient may have a gram-negative rod bacteremia. Most bacteremias occur when the granulocyte count is $<100/\mu l$ and those least likely to respond to antimicrobial therapy are in those with persistence of profound granulocytopenia. I would recommend the use of an antimicrobial combination for these patients. Other patients will probably respond adequately to a single broad spectrum bactericidal agent given promptly in appropriate dosage intravenously. The next set of dilemmas relates to the possible need for alterations in therapy once either microbiologic data become available, along with susceptibility patterns or, in the absence of such data, should the patient not appear to be responding adequately to the initial regimen. In this situation,

a review of the patient's 'epidemiology' can be most useful (e.g. length of granulocytopenia, prior antibiotic therapy, surveillance culture data, etc.), but most important are the results of daily repeat history and physical examination along with appropriately spaced repeat X-rays and diagnostic cultures.

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