EMPIRIC ANTIBACTERIAL THERAPY DURING GRANULOCITOPENIA IN FEBRILE CHILD, INDUCED BY ACUTE LIMPHOBLASTIC LEUKEMIA (ALL)

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Abstract

In this article is discussed the empirical use of antibacterial therapy and addresses the basis of modifications in therapy. Empiric therapy with broad-spectrum antibiotics against Gram-negative bacteremia is necessary in febrile granulocytopenic ALL patients. The level and dynamics of granulocyte count are extremely important in determining the outcome of bacteremia. Most empiric regimens will require therapeutic modifications which contribute to a high overall success rate. Only microbiologically documented infections and especially bacteremias are useful for comparison of initial response to antimicrobial regimens. Gram-positive pathogens have become a common cause of bacteremia in granulocytopenic ALL patients. The response rate to empiric treatment may be suboptimal, but the associated mortality is low. The rational use of antibiotic therapy in children at risk for severe, live-threatening infection represents one of the major advances in the supportive care of children undergoing antineoplastic therapy.

Key words: antibacterial therapy, neutropenia, fever

Introduction

Infection is the most frequent complication of granulocytopenia and when left untreated is often fatal. Since fever is commonly the only symptom of infection in neutropenic patients, the empiric administration of antimicrobials to febrile granulocytopenic patients has become accepted practice. [1] Dramatic progress has been made in the management of febrile children with neutropenia (absolute neutrophile count < 500 neutrophils/μL^3), the single most important risk factor for infection. [2, 3] Today, it is decreasing the chance for children to die from infectious complications during therapy, primarily because of the evolution of supportive care afforded children with neutropenia. [4, 5] These advances in the management of infectious complications have permitted oncologists to treat with higher doses of therapy and to treat more patients on re-induction schema. This, in turn, translates into an expanding number of children with ALL undergoing aggressive therapy who are at risk for infection. [6] The presence of neutropenia is the most important factor associated with infection in the febrile child with cancer.[3, 7] The early institution of empirical antibiotics in the febrile, neutropenic patient has resulted in a marked decrease in morbidity and mortality, even in the absence of either a microbiologic or a clinical diagnosis. [1, 2, 8, 9] Accordingly, the depth and duration of neutropenia are important determinants in assessing the relative risk of a serious infection, guiding decisions to initiate, modify or terminate empirical antibiotic therapy. In the 1990s, the mortality associated with a febrile, neutropenic event is approximately 5%. [3] A number of advances in supportive care are responsible for this trend, including early intervention with new broad-spectrum antibiotics, earlier detection of pathogens, recombinant haematopoietic growth factors, and the recognition of specific clinical syndromes.[6] Still, the fact that mortality has not been completely eliminated underscores the gravity of fever and neutropenia in children with ALL. Because the majority of febrile, neutropenic events do not have a source of infection identified, treatment is administered to many who may not have needed therapy. [5, 9, 10] However, the consequences of observing but not treating can be devastating. [7, 11] The algorithms for treating febrile, neutropenic patients have been based on cancer patients with therapy-induced neutropenia. It is important to recognize that other factors, such as mucositis, suppression of other arms of host defense, specifically, cell-mediated immunity and the presence of indwelling catheters, also contribute to the overall risk of infection. [6]

GENERAL ISSUES OF ANTIBIOTIC CHOICE

Initial empirical therapy:

The choice of antibiotic therapy in febrile neutropenic children should be designed to provide broad coverage for a range of pathogens. Historically, the emphasis has been on providing adequate coverage for treating Gram-negative enteric bacteria and *Pseudomonas aeruginosa*. Because of the significant morbidity and mortality associated with these bacteria, coverage has been directed at these devastating pathogens, even though they may not be the most common. Beginning in the late 1970s, at the same time that long-term indwelling catheters were introduced, a gradual shift of microbiologically determined infections took place. [13] A preponderance of Gram-negative bacteria has given way to Gram-positive organisms. [14-16] Recently, an increase in Gram-negative organisms has been noted, but it is too early to determine if this is a long term shift. Until recently, the standard empirical antibiotic regimen consisted in combination of antibiotics designed to

provide broad coverage and discourage the emergence of resistant organisms. [17] Synergy, improved killing with two antibiotics, provided a rational basis for combination therapy. [18, 19] Many different combinations have been tested, but no particular combination has shown superior efficacy. [20, 21] Nonetheless, partly because of familiarity and partly because of pharmacokinetic considerations, successful combinations that has gained universal acceptance include a β-lactam agent, either an ureidopenicillin or third-generation cephalosporin, and an aminoglycoside. Use of ceftazidime as monotherapy has been substantiated in numerous studies and was recently reviewed in a meta-analysis. [22] The introduction of carbapenams (which include imipenam) offers slightly increase coverage of Gram-positive organisms (e.g. enterococci) and anaerobes. Studies with this agent have confirmed equivalency in overall efficacy compared to either combination therapy of ceftazidime monotherapy. Some authors have raised concerns regarding the use of monotherapy for fever and neutropenia, especially in children, but the theoretical basis of these concerns have been answered by extensive clinical experience. [18, 23] Still, the choice of monotherapy must be made in the context of the unique experiences of the local hospital epidemiology and resistance patterns. However, it cannot be overstated that it is necessary to maintain a flexible approach with regard to selection and modification of an empirical regimen. This mandates frequent and meticulous clinical evaluation of patients daily. Furthermore, the choice of agents for empirical coverage should take into account trends in antibiotic usage and susceptibility patterns of recently isolated pathogens. The success of initial therapy has been predicated on the administration of one or more antimicrobial agents that achieve high serum concentrations. In this regard, the ability to achieve effective bactericidal activity, even in the absence of neutrophils, is critical to the success of therapy. The choice of initial antibiotics should include agents for which the risk of encountering and selecting for resistance is low. For example, one of the motivations for developing third-generations cephalosporins was to counter the emergence of lactamase activity in enteric Gram-negative organisms. However, selected pathogens, such as *Enterobacter* and *Citrobacter spp.*, have emerged which quickly develop resistance during therapy. [24] The choice of antibiotics must also take into account the toxicity profile and the potential for drug interactions. Lastly, the decision to choose antibiotics should also be based upon a demonstrated clinical efficacy. The standard approach has been to continue administering intravenous antibiotics until both the fever and the neutropenia resolve, if neutropenia resist for at least one week. [3, 17, 30] In selected circumstances, fever may be short-lived and yet the neutropenia persists. The recommendation is a minimum of 5 to 7 days of parenteral antibiotics be administered after resolution of fever in patients with protracted neutropenia. [17] Several preliminary studies have attempted to shorten the duration of empirical antibiotics in children with prolonged neutropenia. [31-33] In fact, children were discharged from the hospital with no antibiotic therapy, if they became afebrile quickly and had no microbiologic or clinical diagnosis made. However, the studies are small and the numbers insufficient to establish this approach for all patients. The application of early discharge does have its proponents who argue that the determination of low- and high-risk patients should be adequate for tailoring continuation therapy or discontinuing therapy. [34] They suggest that "low-risk" patients should be discharged early if all cultures are unremarkable, fever has abated, a short period of neutropenia is anticipated and easy access to care is available. [31-33, 35, 36] Ongoing studies with oral antibiotics may lead to more cost-effective strategies, but this approach, too, is investigational. If a microbiologically or clinically diagnosis is made, the duration of therapy should err on the longer side. In other words, if *Klepsiella pneumoniae* sepsis is diagnosed in neutropenic child, therapy for at least two weeks with intravenous antibiotics or until neutrophils recover is indicated, whichever is longer. If clinically indicated, oral antibiotics can be successfully used to complete therapy, once neutropenia has resolved.

Modification of initial coverage:

Independent of the initial choice of empirical antibiotics for management of the febrile, neutropenic child, it is important to recognize that modifications of the primary agents will be necessary, particularly the longer a patients remains neutropenic, This is especially true in patients with a clinical or microbiologic diagnosis. Generally, during the first 5 to 7 days, modifications are made in response to the susceptibility pattern of an isolated pathogen or a clinically identified problem, such as a perirectal focus of infection. The decision to add anaerobic coverage for severe mucositis should be predicated on severity of lesions. Generally, the addition of clindamycin or metronidazole should be reserved for serious lesions with necrosis or foul-smelling odor. On occasion, a breakthrough or a resistant organism will require modification of the initial empiric antibiotic therapy. Still, the persistence of fever is not necessarily an indication to alter coverage. In patients with protracted neutropenia, fever is commonplace, in spite of broad-spectrum antibacterial coverage. However, the presence of persistent fever is an important warning sign that necessitates careful and continual investigation; yet in a substantial majority of patients, no new etiology will be identified. The likelihood of a documented infection is greatest at the time of presentation. In roughly one-third of patients a specific clinical syndrome or a microbiologically isolated pathogen will be diagnosed within days of presentation with fever and neutropenia. [9] However, the recurrence of fever after several days or the persistence of fever for 5 or more days is an indicator of increased risk. [7]

Preventive strategies:

Over the past 25 years, a number of preventive strategies have been investigated in patients with cancer. Some have been designed to protect the neutropenic patients from acquiring new pathogenic bacteria. The basic principle

underlying this approach is to isolate the patient from new potential pathogens. This strategy has had many proponents who have used such measures as complete isolation and a sterile room with filtered air and protective barriers including masks, gloves and gowns. Variations of this theme include neutropenic diets, avoidance of public places during both of neutropenia, reverse precautions or single rooms. Above all, the most important measure includes good handwashing before and after examining neutropenic children. Another parallel approach has been to administer prophylactic or preventive antibiotics to reduce or eliminate endogenous bacteria, considered to be dangerous opportunistic pathogens in the immuno-compromised host. This approach referred to as selective gut decontamination, is based on the principle of affecting colonization resistance patterns. [38, 39] Over time, successive studies with non-absorbable agents trimethoprim / sulfamethoxazole, and recently fluoroquinolones have been conducted. [40, 41] Unfortunately, the success of each of these strategies has not been impressive, especially when one considers the cost, toxicity and selection of resistant organisms. Furthermore, delays in recovery of bone marrow, skin rashes and selection of fungal and multiply-resistant bacteria are major side effects. It is noteworthy that trimethoprim / sulfamethoxazole is an excellent choice for prophylaxis against *Pneumocystis carinii* pneumonia, especially in children with leukemia receiving consolidation or maintenance therapy. [42] Trends have shifted from the use of total protective precautions to the use of prophylactic antibiotics but with little impact on the incidence or severity of infection. The use of prophylactic fluoroquinolones reached its limits in the early 1990s but with the emergence of resistant organisms the trend has been to shy away from this strategy. For the most part, fluoroquinolone prophylaxis should be reserved for special circumstances and not used routinely in all neutropenic patients at risk for infection.

SPECIFIC ANTIMICROBIAL AGENTS

Third-generation cephalosporins:

By the early 1990s, extensive experience with ceftazidime alone established the efficacy of monotherapy in the febrile, neutropenic patients. Ceftazidime is well suited for this purpose, primarily on account of its broad spectrum of activity, including excellent minimum inhibitory concentrations against *P. aeruginosa* as well as enteric Gram-negative organisms. Cefaperazone, the other commercially available third-generation cephalosporin with comparable activity has been shown to be effective in combination therapy. Its use as monotherapy has been limited. Both drugs have excellent tissue penetration, including the cerebrospinal fluid (which is rarely the site of infection in neutropenic patients but when present can be devastating). The toxicity profiles for both drugs are favorable and unlike other third-generation cephalosporins, it does not interfere with the coagulation pathways. The decision to use ceftriaxone in pediatric cancer patients is complex and is not recommended at this time. Despite the advantage of once a day administration, the lack of activity against *P. aeruginosa* and other Gram-negative enteric bacteria prevents the recommendation of ceftriaxone as first-line therapy. Ceftazidime has attained the designation of "standard of therapy" for monotherapy. [3, 9, 23] A large, prospective randomized controlled study established efficacy comparable to combination therapy. [9] If ceftazidime is chosen as monotherapy, the clinician must be willing to modify therapy quickly when indicated by either microbiologic results or clinical changes in the febrile, neutropenic child. [37] The ability to administer a single agent offers a number of advantages but also requires close observation during the course of therapy. In this regard, it is not appropriate to use ceftazidime as an outpatient or home infusion antibiotic for a febrile neutropenic event. One attractive advantage of ceftazidime monotherapy is that it eliminates the risks, cost and need to monitor serum levels of aminoglycosides.

Carbapenem:

Imipenem is a member of Carbapenem class of antibiotics, offering a second comparable choice for empirical monotherapy. [37, 43] Its spectrum of activity extends beyond the range of ceftazidime and includes improved coverage for enterococci and many anaerobes. It has favorable pharmacokinetics, shows excellent activity against the primary pathogens and is relatively well-tolerated. It has been used successfully in febrile, neutropenic children with cancer. [37, 44] compared to ceftazidime, it has more gastro-intestinal toxicity, specifically, nausea, diarrhea and *Clostridium difficile* colitis and did not significantly decrease the overall need for antibiotic modification. [37] A number of individual studies have established its efficacy, showing that it is equivalent to either ceftazidime monotherapy or combination therapy. [37, 43] The problem of gastrointestinal toxicity associated with imipenem is an important factor for choosing between ceftazidime and imipenem. For this reason alone, it may be prudent to start with ceftazidime for monotherapy and use imipenem for patients who show signs of cardiovascular instability or breakthrough / resistant infection. Meropenem is a new agent with great potential. Preliminary data suggest it is safe and probably equivalent wipenem but with less toxicity. Studies in children are ongoing at this time.

Aminoglycosides:

Aminoglycosides were once considered essential agents in the empirical management of febrile, neutropenic patients, primarily because of their excellent activity against Gram-negative enteric bacteria and Pseudomonas spp. At one time, it was inconceivable to start therapy without an aminoglycoside. This approach arose from both clinical experience and was justified by the *in vitro* observation that the combination of a β-lactam agent and an aminoglycoside resulted in a synergistic microbicidal effect. Monotherapy with imipenem or ceftazidime has been shown to be both safe and efficient and thus, aminoglycoside therapy has been

relegated to a secondary role. Even the use of a short course of aminoglycosides has been shown to provide only a marginal advantage for survival in patients with a documented Gram-negative bacteremia. [45] In the large randomized study that established the efficacy of ceftazidime monotherapy, an analysis of the modifications revealed a significant overuse of aminoglycosides. In the 1990s, aminoglycosides have marginal utility for initial therapy in the febrile, neutropenic patient. In truth, aminoglycoside therapy is best used for pathogen-specific indications. In this regard, the use of aminoglycosides in the initial management of the febrile, neutropenic child should be reserved for those children in whom combination therapy with either a ureidoor carboxypenicillin is required or an intravenous fluoroquinolone is indicated (because of a drug allergy to β-lactamase agents). The former may be necessary because of a high incidence of infections in the local institution with Gram-negative organisms that are resistant to β-lactams or develop resistance during monotherapy (e.g. Enterobacter spp., Acinetobacter spp. and Pseudomonas spp.). Aminoglycosides should be included in the initial therapy for neutropenic child who exhibits cardiac instability or hypertension. In a similar manner, use is indicated in patients already receiving therapy who suddenly develop signs and symptoms of sepsis.

Aztreonam:

Aztreonam is a monobactam antibiotic that is highly resistant to most β-lactams. Its spectrum of activity is comparable to that of the aminoglycosides, it is active against Gram-negative enteric bacteria but does not have significant renal toxicity and ototoxicity. Combined with vancomycin, it has been used successfully in the empirical treatment of febrile, neutropenic cancer patient in a small uncontrolled study. [46] However, aztreonam lacks synergy with β-lactams against Gram-negative enteric bacteria. Because of its poor activity against Gram-positive and anaerobic bacteria and its cost, its use is limited to substitution for an aminoglycoside in a child with renal disease / toxicity, a highly resistant organism or a severe penicillin allergy. [59]

Fluoroquinolones:

The fluoroquinolones offer excellent coverage for Gram-negative enteric bacteria and have favorable pharmacokinetics suitable for either oral or intravenous administration. [47] There is little compelling data to support monotherapy with a fluoroquinolone, especially in children. [48] This is based upon lack of efficacy and the emergence of resistant strains of Gram-negative enteric bacteria. On occasion, fluoroquinolones have been used to successfully treat multiply-resistant organisms for which few or no other antibiotics are available. [21] In addition the poor coverage for Gram-positive organisms, especially staphylococcal and streptococcal species, makes this class of agents unsuitable for monotherapy. Several outbreaks of pathogenic, resistant coagulase-negative staphylococci infection have been reported in oncology centers where fluoroquinolones are commonly administered for prophylaxis. [49] Moreover, breakthrough with life-threatening streptococcal infections has emerged as a major complication in patients receiving fluoroquinolones as a single prophylactic agent during prolonged neutropenia. For treatment of febrile, neutropenic patients, fluoroquinolones may be a suitable agent for use in β-lactam-allergic patients but in combination with an aminoglycoside. Excellent oral bioavailability is a distinct advantage for treatment of low-risk febrile, neutropenic patients as outpatients. Studies are ongoing to address whether this strategy is safe and efficient. Despite the paucity of published data, many practicing adult oncologists have adopted this practice for low-risk patients, usually in combination with other agent with extended Gram-positive coverage, such as ampicillin / sulbactam. At the same time, fluoroquinolone usage in children, originally discouraged by animal data suggesting an injurious effect on bone / cartilage development, is increasing. Recently, a subcommittee of the International Society of Chemotherapy endorsed the use of fluoroquinolones in children with severe infections, especially when an alternative safe therapy is not available. Until conclusive studies demonstrate that early discharge of febrile neutropenic patients treated with oral fluoroquinolones is safe, it is unlikely that fluoroquinolones will be considered the first-line choice for febrile, neutropenic children. Fluoroquinolones have been shown to be effective when administered as prophylactic antibiotics during periods of neutropenia. However, the selection of resistant organisms represents a powerful deterrent for this practice in all but selected circumstances. On a theoretical basis, one could argue that they may be useful for prophylaxis during the recovery phase from a bone marrow transplant. The distinct advantage in this setting is that the patient is not repeatedly exposed to fluoroquinolones and in this regard, selection of resistant organism is minimized. Repeated uses encourage not only the emergence of newly acquired resistance but also the selection of organisms, such as α-streptococci, which may be devastating in the intensively treated patient.

Vancomycin:

Because of the emergence of Gram-positive organisms as the most commonly encountered clinical isolate in febrile, neutropenic children, vancomycin usage is common in pediatric oncology. [13, 16] Since it is the most effective agent against non-aureus staphylococci, enterococci and α-streptococci, three important pathogens in the immuno-compromised child, it is a primary choice for documented infections with the above pathogens (pending sensitivities). Often, one or more of these pathogens cause a catheter-associated bacteremia, even in the non-neutropenic child. Vancomycin is administered as an intravenous bolus and levels are frequently measured to establish adequate dosage. Its spectrum is limited to Gram-positive organisms. Another glycopeptide, teicoplanin offers a similar spectrum of activity but the clinical experience with this agent is limited compared to vancomycin. Some have recommended

that vancomycin be added to the up-front empirical regimen and in fact, many centers have adopted this approach. [25, 26, 28] Conversely, it has been argued that vancomycin should be withheld until the Gram-positive isolate has been identified microbiologically since most of these organisms are of low virulence and inhibited by β-lactam antibiotics. [27] On the other hand, Karp et al. [26] showed that the incidence of the secondary Gram-positive infections was decreased in patients who received empirical vancomycin with initial therapy. The routine administration of empirical vancomycin would have over treated nearly 95% of patients. Out of concern for the burgeoning problem of vancomycin resistance in enterococci, one has to consider the importance of withholding this agent until a microbiologic diagnosis is made. In conclusion, the routine inclusion of vancomycin in initial empirical therapy is not indicated, but it should be held in reserve for pathogen-specific usage. Again, local institutional patterns of susceptibilities and isolated organisms may require reconsideration of this approach.

Conclusions

The judicious use of empirical antibacterial therapy in the pediatric patient with fever and neutropenia has contributed significantly to improvements in the management of infectious complications of antineoplastic therapy. Indeed, the use of new, broad-spectrum antibiotics as monotherapy has eliminated more troublesome combinations while providing comparable success of therapy. The goal of next decade will be to develop strategies using recombinant growth factors (for well-defined indications), molecular diagnostics and the selective use of available antibiotics to refine the approach to treating the febrile, neutropenic child. At the same time, it is imperative that we better define the pleiotropic effects of chemotherapy and other limbs of the immune system. The success of supportive care (especially of infectious complications) has permitted oncologists to push the limits of toxicity (e.g. risk of infection) and consequently created a larger number of children at risk. Present controversies include not only the choice of antibiotics, both at initiation and in response to either microbiologically isolated pathogens or clinical syndromes, but also the duration and mode of administration (intravenous versus oral). The optimal use of biologic modifiers and recombinant growth factors remains to be determined. [50] They should not be used indiscriminately in children, but when the risk of a serious infectious complication is well-defined, such as following ablative therapy and rescue with either bone marrow or peripheral stem cells. The crisis of resistant organisms is a sobering reality that challenges the specialist to assess the indication for using antibiotic therapy. Most experts would agree that the trend in the future will be to limit the use of antibiotics as a measure to minimize the emergence of resistant organisms but also as a cost-saving measure. For this strategy to be effective, we will need to develop algorithms to refining risk groups and basing treatment decisions accordingly. [11] Lastly, the controversies regarding the choice and modification schemes for antibiotic intervention need to be viewed in the context of the individual patient. In the end, the patient bears the consequences of the clinician's choice of therapy. The clinician must determine the acceptable risks and benefits of not only initiating therapy but also modifying and terminating therapy for infectious complications in the child receiving ALL therapy.

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