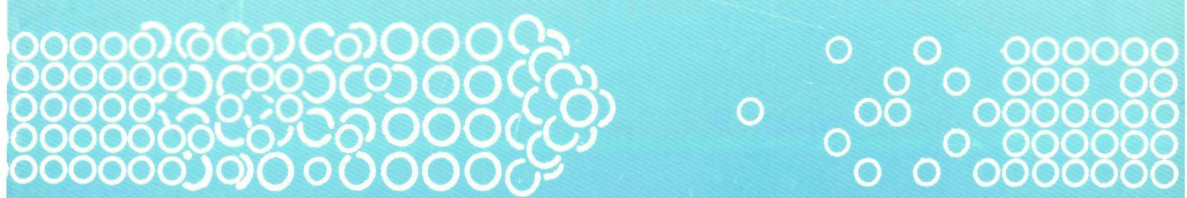
TREATMENT OF BACTERIOLOGICAL INFECTIONS IN NEUTROPENIC PATIENTS WITH SPECIAL EMPHASIS ON CEFTAZIDIME MONOTHERAPY



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PROEFSCHRIFT

TER VERKRIJGING VAN DE GRAAD VAN DOCTOR
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"We all must die.
But if I can save him from days of torture,
that is what I feel is my great and ever new privilege.
Pain is a more terrible lord of mankind
than even death himself."

Albert Schweitzer

Aan onze Ouders,
Mieke en onze Kinderen

The studies presented in this thesis were performed in the division of Hematology, Department of Internal Medicine, University Hospital, Sint Radboud, Nijmegen, The Netherlands.

CONTENTS

CHAPTER 1
INTRODUCTION

Since the chemotherapeutic treatment of haematological malignancies and solid tumors is becoming more aggressive and effective, an increasing number of patients will be at risk for granulocytopenia. Consequently, the improved outlook for these patients is jeopardized by the threat of infection. Next to neutropenia, many other factors may predispose these patients to infection with a wide variety of pathogens. Therefore, measures designed to prevent infections by reducing the risk of acquisition of potential pathogens and by preserving natural anatomic barriers, or early adequate therapy in case of infection, have been stressed in the literature. There is no doubt, that the last decade has witnessed an enormous improvement in the successful management of infectious complications in immunocompromised patients. Though changing medical practices contribute to the emergence of new pathogens and necessitate the development of new antimicrobial agents continuously.

MAGNITUDE OF THE PROBLEM

Although the advanced management of neoplastic diseases has increased the chance of "disease free survival", the majority of adult patients with acute leukemia are dying due to complications of chemotherapy during remission induction or maintenance therapy. Autopsy data from different centers show a remarkably stable incidence of infection as a major cause of death during the last 3 decades (see Table 1). Bleeding disorders, which have been the second major cause of mortality in these patients, is declining gradually; from 54% in the period 1954-1963 to 36% in the last decade. This may be attributed to the development of effective platelets transfusions (3). Between 1972 and 1985, in St. Radboud hospital (Nijmegen), 50% of the mortality in patients with acute leukemia was due to infection and 43% due to bleeding disorders.

Table 1 Causes of death among patients with acute leukemia.

Reference	Period	Number of patients	Principal causes of death (%) Haemorrhage*	Infection**	Other
(1)	1954-1963	354	54%	72%	13%
(2)	1966-1972	315	24%	74%	10%
(3)	1976-1982	109	36%	68%	10%
Nijmegen**	1972-1985	290	43%	50%	17%

* Including haemorrhage accompanied by infection and other causes
** Including infection accompanied by haemorrhage and other causes
** Not published data

FACTORS PREDISPOSING TO INFECTION

Granulocytopenia is the single most prominent risk factor for infection. In addition to the actual granulocyte count (4), the duration and persistence of granulocytopenia (5), the functional integrity of the phagocytic system (6), antibody production, impairment of cell-mediated immunity (7) and disturbance of the physical defence barriers are important variables. Under normal circumstances a complex interrelationship of lymphocytes, neutrophils, macrophages, immunoglobulins, complement, and physical barriers provide protection against infecting organisms. Any qualitative or quantitative defect in one of these factors may predispose to infection. Defects may be disease related, as in haematological malignancies (8) and graft-versus-host disease after bone marrow transplantation (9,10), or secondary to treatment with irradiation and/or cytostatic drugs. The quantitative effects of these treatment modalities on the haematopoetic system are well recognized, but they also enhance the risk of infection by interference with the function of the remaining immunocompetent cells (11,12), and the integrity of the mucous membranes. Another port of entry may be the skin, as the vast majority of patients will have peripheral or central catheters (13) for administration of the cytostatic drugs and supportive therapy. A major source of infection is the endogenous gut flora of the patient. Colonization precedes infection (14) and admission alone increases the chance of acquiring potentially pathogenic strains (15,16). Van der Waaij et al (17,18) have shown that preservation of the endogenous anaerobic microorganisms, that compose up to 99% of the gut flora, attribute to the resistance against colonization by transient,

potentially pathogenic germs.

Finally it has to be mentioned that immunocompromised patients show an increased susceptibility for transmission of infectious agents by blood products, contaminated intravenous fluids (19,20), foods, visitors and medical attendants (21). The spectrum of these infections is wide, including bacteria, viruses and fungi. It may be clear that not all granulocytopenic patients have the same risk of infection. Differences in the degree of impairment in neutrophilic and non-neutrophilic defences and differences in environmental circumstances may determine whether or not a granulocytopenic patient will become infected.

SPECTRUM OF INFECTING PATHOGENS

A minority of infections in the neutropenic patient are community acquired. In a retrospective analysis of all patients suffering from acute leukemia treated in our clinic between 1975-1985, we found a microbiologically proven infection in 19% on first admission. The organisms found were similar to those causing infections in normal hosts, but there was a difference in terms of severity and duration. Gram-positive infections were mainly due to *Staphylococcus aureus* (20%) and less frequently to *Streptococcus pyogenus* or to *Strep. pneumoniae*. Of all Gram-negative infections the predominant isolate was *Escherichia coli* (14%). Incidentally *Klebsiella*, *Enterobacter*, *Proteus* species or *Pseudomonas aeruginosa* were cultured. Twenty per cent of the community acquired infections were polymicrobial and 14% proved to be oral candidosis.

Hospital acquired infections occurred in 74% of the patients during induction and maintenance therapy, with an average of 1.5 infections per patient, (see Table 2). Septicemia and other infections due to *Staphylococcus epidermidis*, viridans streptococci and enterococci emerge in patients who have been hospitalized for some time. *Staphylococcus epidermidis* grown in blood cultures from patients with indwelling intravenous catheters should not be assumed to be a contaminant and may often be the cause of a genuine infection (22). This also holds true for *Corynebacterium* species, often refered to as "diphtheroids" (23). Superinfection with enterococci is a new and increasing problem. Although the mortality rate of these latter infections is rather low (24), the morbidity and costs of prolonged hospitalization and additional antibiotics should not be neglected.

The later occurring Gram-negative infections are mainly higly resistant enterobacteriaceae (see Table 2). The specific organisms most likely to be involved in nosocomial infections depends on the given infection pattern in a specific hospital or even a given ward or patient group (3).

Non-bacterial infections are more likely to occur later during

Table 2 Microbiologically proven infections in 270 patients with acute leukemia admitted from 1975-1985 St. Radboud hospital.

Pathogens	Total (%)	Microorganisms	
Gram-positive	197 (41%)	*Staphylococcus epidermidis*	80 (40%)
		Staphylococcus aureus	54 (27%)
		Streptococcus viridans	21 (11%)
		Beta hemolytic *streptococci*	15 (8%)
		Streptococcus faecalis	10 (5%)
		Streptococcus pneumoniae	9 (5%)
		miscellaneous	8 (4%)
Gram-negative	131 (28%)	*Escherichia coli*	43 (33%)
		Klebsiella species	30 (23%)
		Pseudomonas species	26 (20%)
		Enterobacter species	14 (10%)
		Proteus species	5 (4%)
		miscellaneous	13 (10%)
Anaerobes	4 (1%)		
Polymicrobial	70 (15%)		
Mycosis	71 (15%)	*Candida* species	66 (93%)
		Aspergillus species	3 (4%)
		Torulopsis species	2 (3%)

therapy. Fungal infections have to be considered when an antibiotic induced defervescense is followed by a new episode of fever, particularly in those patients in whom no bacterial cause could be identified. Invasive candidosis and aspergillosis are likely to occur in this setting and high mortality rates have to be expected (25-27). Transfusion associated hepatitis A and B may run a fulminant course (28). Patients, who have additional impaired cellular immunity are at great risk of reactivating or acquiring a herpes virus infection (29,30). Cytomegalovirus infections may induce life threatening illness in immunocompromised patients (10). Interstitial pneumonitis, manifesting itself as fever, dyspnoe and dry cough, is one of the most feared complications after bone marrow

transplantation (9,31). The majority of cytomegalovirus infections is related to administration of blood products, especially leukocytes (32). Less frequent, but dangerous complications are infections by *Toxoplasma gondii* and *Pneumocystes carinii* , particularly if the immunocompromised patient is being treated with corticosteroids (33).

PREVENTION OF INFECTION

Since the majority of infecting organisms in immunosuppressed patients arise from the endogenous microbial flora, eventually acquired during the patients hospitalization, it is not surprising that nursing in reverse isolation is only of limited value (34). Maximal reduction in microbial contamination of the patient and his environment by the use of laminar air flow or filtered air, specially prepared food, and skin cleansing agents will prevent a small minority of the infections but may be accompanied by a considerable discomfort for the patients (35-37). Simple avoidance of contact with overt or well-known sources of infection seems to be sufficient in most cases (34).

During the last decade oral nonabsorbable antibiotics have formed the backbone of the infection prevention regimens in order to reduce the endogenous microbial burden (38). Although there is a rational basis for this approach, studies performed until now have not shown that the use of oral nonabsorbable antibiotics alone has a definite and constantly positive effect in the prevention of infection. Next to the poor patient compliance with these antibiotics, suppresion rather than elimination of the endogenous flora is achieved, with the risk of rapid repopulation by virulent organisms and subsequent infection following accidently premature discontinuation. The importance of attempting to sterilize the gastrointestinal tract completely has been questioned by van der Waaij (39). He introduced as an alternative, partial decontamination or selective manipulation of the gut flora. He and his coworkers demonstrated that preservation of the host's anaerobic flora provides a resistance to colonization by exogenous aerobic potential pathogenic organisms. Several antibiotics (co-trimoxazole, quinolones, polymyxins and low-dose aminoglycosides) are able to eradicate aerobic Gram-negative organisms and part of the staphylococci and miconazole, ketoconazole or amphotericin B are able to reduce fungi, while preserving the gastrointestinal anaerobes.

The concept of colonization resistance has been tested successfully in leukemia patients undergoing bone marrow ablative chemotherapy (18). The results are encouraging, but infections are not eliminated completely. For instance, food known to be highly contaminated by Gram-negative bacilli should be avoided at all time (40,41). Moreover, application of co-trimoxazole alone has been associated with increased incidence of fungal infections (42), colonization and subsequent infection by resistant enterobacteriaceae (43-45) and prolongation of the granulocytopenia (46). Successful application of this approach requires combination therapy and close microbiological surveillance, so that the antibiotic regimen can be adjusted continously when new and/or drug-resistant organisms appear. This is both labor intensive and expensive. On the other hand, the clinical value of these surveillance cultures for identification of an organism responsible for a febrile period is low (47). Reviewing the infections occurring during the past decade at our haematological ward, we were able to predict the causative pathogen on the basis of surveillance cultures in 8 out of 473 cases and in only one case this putative knowledge did have implications for the empiric therapy.

Several antimicrobial agents are under investigation as prophylaxis against specific infections which are common among the immunocompromised host. Co-trimoxazole was established to be capable of reducing the frequency of *Pneumocystis carinii* infections in highly susceptible patients (48). Acyclovir has been used successfully as prophylaxis against herpes virus infections in bone marrow transplant recipients (49). In our institute we have good experiences with cephaloridin suspension as a gargle to prevent colonization of the oropharynx by staphylococci. However application seems to be associated with an increased incidence of fungal infections.

Profylactic administration of granulocyte transfusions to bridge the neutropenic period has been investigated. In most studies the results were disappointing (50). Moreover, a higher incidence of cytomegalovirus infections was registered in recipients of granulocyte transfusions (32).

Both active and passive immunotherapeutic measures have been evaluated for protecting patients from infectious complications. Active immunotherapy may be hampered not only by the impaired antibody response due to the underlying haematological disease, but also by the concomitant immunosuppressive chemotherapy. Passive immunotherapy lacks this disadvantage and studies are being conducted with Pseudomonas antiserum,

anticytomegalovirus hyperimune globulins and antiserum to the core glycolipid of Gram-negative bacteria or diphtheroids (51). The possibilities and limitations of manipulating the immuneresponse by transfer factor or interferon are still under investigation.

DIAGNOSIS OF INFECTION IN GRANULOCYTOPENIC PATIENTS

Despite profylactic measurements the majority of neutropenic patients will develop infections. The classic symptoms of inflammation (dolor, rubor, calor, tumor and functio laesa) are less clear in the patient with neutropenia. Especially fluctuation, exudation and ulceration are more closely related to the presence of granulocytes and may be reduced remarkably. But erythema may occur and pain and fever remains a reliable indication of a localized infection (52). Besides fever, positive physical examination or infiltrates on a chest x-ray may be indicative of pneumonia even in the absence of cough or sputum production.

A continuing problem is the very high proportion of "infections" that never are documented microbiologically. Fevers of unknown origin may account for more than 50% of the febrile episodes (6). More aggressive investigation like bronchoscopy or open lung biopsy has only benefited a minority of patients (53-55). Moreover, fungal infection is hard to prove and the majority have been discovered after autopsy only (56). Serum conversion in case of viral infections may be absent due to the impaired immune system of these patients.

The decision to initiate antimicrobial therapy must be based on substantially less hard data than in patients with a normal granulocyte count. Because it does not appear to be possible to determine reliably the granulocytopenic patient whose fever has an infectious origin, it seems best to assume that all patients who become febrile when the leucocyte count is less than $1000/mm^3$ are infected until proven otherwise.

EMPIRIC TREATMENT OF THE FEBRILE GRANULOCYTOPENIC PATIENT

Antimicrobial therapy in febrile neutropenic patients should be undertaken on an empirical basis, i.e. pending the results of the cultures. If adequate therapy is delayed, awaiting microbiological confirmation, more

than half of the patients with an infection due to Gram-negative organisms will die during the first 48 hours (57). The primary objective of initial empiric therapy is to protect these patients from early death. Therefore, the antibiotic regimen selected must be active against the major pathogens and in particular against Gram-negative bacilli. The incidence of infections due to Gram-positive organisms is increasing (22,58). In our institute the ratio Gram-positive/negative pathogens has increased from 0.87 in 1975 to 3.2 in 1985. Despite the increased morbidity due to Gram-positive bacilli, still half of the mortality in patients with acute leukemia dying from a bacterial infection, are caused by Gram-negative pathogens (See Table 3).

Table 3 Fatal Infections in Acute Leukemia (St. Radboud Hospital).

Origin / Period	Bacterial infections Gram +	Gram -	Poly-microbial	Mycotic-infection	No isolate
Pneumonia					
1972-1978	1 (3%)	8 (24%)	-	5 (15%)	19 (58%)
1979-1985	3 (7%)	5 (12%)	-	16 (37%)	19 (44%)
Septicemia					
1972-1978	4 (19%)	16 (76%)	1 (5%)	-	-
1979-1985	14 (46%)	12 (40%)	2 (7%)	2 (7%)	-

Infections caused by Gram-positive cocci are normally less aggressive and, consequently, offer more opportunity to adjust the antibiotic treatment scheme according to the sensitivity spectrum of the isolated microorganism(s). Despite their numbers, anaerobic bacteria rarely cause primary infection in granulocytopenic patients (Table 2). Fungi, particularly candida species, can be a primary cause, but are more likely to be a problem in patients with protracted neutropenia who already have been treated with antibiotics (59,60).

It is important to stress that the efficacy of an empiric antibiotic regimen must be evaluated for both initial treatment (the first 72 hours) and during the complete period of persisting granulocytopenia. Patients with extended granulocytopenia are at risk for secondary infectious complication and this risk is increasing with the duration of neutropenia, including resistant bacteria as well as nonbacterial pathogens.

Initial empiric therapy traditionally consists of a two- or three drug regimen, usually comprising an aminoglycoside, a cephalosporin and/or

an antipseudomonal penicillin (61-91). Selection criteria are based on bactericidal spectrum, possible synergism, side effects and costs. No absolute superior combination has been described in a large number of trials (See Table 4). It seems appropriate to consider the susceptibility pattern in a given hospital or ward in determining the combination of choice. In the past it has been shown, that the success rate for Gram-negative bacteremia will increase if the isolate is susceptible to both antibiotics in the treatment regimen, compared to those infections in which the susceptibility of the isolated pathogen is restricted to one of the drugs alone (57,92). Another important aspect of initial antimicrobial therapy is the emergence of *Staphylococcus epidermidis* associated with intravascular devices as an important pathogen with unpredictable susceptibility. Inclusion of broad spectrum anti-staphylococcal antibiotics in the initial regimen may be necessary in those cases.

Table 4 Antibiotics and combination of antibiotics in the empiric treatment of febrile neutropenic patients 1972-1986.

Drug regimen	References	Number episodes	Outcome range (%)
Three drug regimen			
Pen. + Ceph. + Aminogl.	72,77,83,84	485	57-67%
Pen. + Vanc. + Aminogl.	78	23*	74%
Monob. + Vanc. + Aminogl.	81	155*	72%
Two drug regimen			
Pen. + Aminogl.	61,63-68,77,78,82,88,89,91	2543	49-97%
Ceph. + Aminogl.	63,68-71,73-75,82,86,87,91	1072	47-83%
Pen. + Ceph.	61-64,71,74,79-81,86,91	1392	48-77%
Monob. + Vanc.	81	155*	69%
Pen. + Vanc.	66	193*	65%
Ceph. + Vanc.	84	37*	57%
Monotherapy			
Ceftazidime	69,70,72,79,83,84	480	43-80%
Moxalactam	73	29*	73%
Imipenem (+ cilastin)	85	79*	67%
Cefoperazone	87	22*	71%
Gentamicin	91	122*	22-53%

Pen = Broadspectrum-penicillin, Ceph. = Cephalosporin, Monob. = Monobactam, Aminogl. = Aminoglycoside, Vanc. = Vancomycin.

* Single study.

Each antibiotic, which is used in the treatment of febrile neutropenic patients has its own benefits and disadvantages. All major classes of antimicrobials: aminoglycosides, cephalosporins, and extended spectrum penicillins, meet the prerequisite of sufficient bactericidal activity (93). The use of aminoglycosides is associated with the risk of ototoxicity and nephrotoxicity, especially when repeated courses are necessary or if applied in combination with other potentially toxic drugs (94-96). The dose should be adjusted individually. Moreover, the efficacy of aminoglycosides depends on the severity of neutropenia. Without synergistic additional therapy no reliable activity in severely neutropenic patients can be expected (90,97). The older cephalosporins have a gap in activity against Gram-negative organisms, whereas the last generation shows suboptimal activity against Gram-positive cocci. They all lack useful activity against enterococci (98). The anti-anaerobic activity of the antipseudomonal penicillins is a major disadvantage with respect to the colonization resistance. Other side effects of these drugs are the higher incidence of allergy, prolongation of neutropenia, hypokalemia, interference with bloodclotting and high sodium content (65,71,99).

The choice of an initial antimicrobial agent is not the only problem in the treatment of febrile neutropenic patients. Duration of a successful therapy and the attitude towards persistant fever are still controversial. It is an accepted policy now to narrow the spectrum of the antibiotic regimen in normal patients, as soon as the causative organism has been identified, avoiding unnecessary toxicity and risk of superinfection. However, in the neutropenic patient continuation of the broadspectrum antibiotics seems to be preferable, since they provide systemic prophylaxis. The incidence of superinfections and relapses is reduced if the antibiotic treatment is continued (100). It is our policy to continue the antibiotic therapy in the successfully treated patients until 2 days after subsidence of all symptoms in cases where the granulocytes are increasing, and for 4 days if no increase in the granulocyte count is registered. During treatment, the selective gut decontamination is continued if feasible. If not, it is resumed as soon as possible until granulocyte recovery.

The issue is much more complex for the persistently granulocytopenic patient who remains febrile without demonstrable infection. One tends to switch antibiotics on the assumption that lasting fever represents an inadequate response or the emergence of resistant organisms. However, fever

may be worrisome, but in the absence of a deteriorating clinical condition, it does not necessarily reflect failure. The first step could be additional therapy against bacilli not covered by the initial empiric combination. In case of progressive mucositis or perirectal tenderness addition of an anti-anaerobic drug may be considered. Antifungal therapy should be initiated empirically in neutropenic patients remaining febrile after broad-spectrum antibiotics in view of the risk of invasive fungal disease (101). If the adjustments of the antibiotic scheme do not induce defervescence, cessation of therapy seems warranted in order to avoid toxicity, risk of resistant superinfections and to save expenses, premising the patients condition is not poor or deteriorating.

Another tenet of infection management is that foreign bodies like indwelling catheters, which are regularly used in these patients, should be removed when fever persists. In case of Gram-negative or fungal infections associated with intravenous devices this is most likely the only way to cure the patient. But in case of Gram-positive infections or fever of unknown origin an attempt to save the catheter may be well successful and justifiable (102,103).

THE PLACE OF CEFTAZIDIME MONOTHERAPY IN FEBRILE NEUTROPENIC PATIENTS

The benefits of employing a combination of antibiotics have to be balanced against the additional risk of toxicity. Whether combination therapy, aiming at synergy, remains necessary is currently of interest in the light of the availability of the third generation cephalosporins and carbapenems. In studies of synergistic combination therapy in neutropenic patients Klastersky et al stated that a titre of 16 or more was associated with a better outcome (57,92). These new antibiotics achieve serum levels over 100 fold higher than the minimal inhibitory and bactericidal concentrations for Gram-negative bacteria. Their spectrum of activity includes *Pseudomonas aeruginosa*, Serratia, *Citrobacter*, *Proteus* species and to a lesser extend *Enterobacter cloacae*. The cephalosporins are less active against the staphylococci and streptococci and none achieve an effective serum level against enterococci.

Ceftazidime, one of the "third generation" cephalosporins, is highly resistant to beta-lactamases (104) and has a broad spectrum of in vitro antibacterial activity (97,105). It is less effective against Gram-positive

organisms than imipenem, but has a higher activity against Pseudomonas species. Oral absorption is negligible and intravenous route is preferred. Peak ceftazidime serum concentrations of 70-72 mg/L are attained immediately after one gram (30 minutes) infusion. Mean peak levels between 20-30 mg/L are achieved in a variety of tissues and body fluids. The volume of distribution is ussually between 15 and 20 L. The elimination half-life is 1.5-2.8 hrs. in healthy subjects. Apparently no metabolization occurs and the drug is eliminated largely by glomerular filtration. The half-life is prolonged in patients with moderate to severe renal impairment. Ceftazidime is generally well tolerated. The most commonly reported side effects are transient elevation of liver function tests (3.5-7%), positive Coombs without signs of haemolysis (4.7%), skin rash (1.6-2.7%), and less frequently gastrointestinal reactions (2.4%). Discontinuation of therapy was necessary in 2.4% overall (106).

Faced by the poor results of the combination gentamicin plus cefotaxim (in use in 1980 in our clinic) as empiric treatment of febrile neutropenic patients, and the favourable results achieved by ceftazidime alone in patients who failed on the initial combination, a prospective study was performed to compare these two regimens (69). Ceftazidime monotherapy proved to be significantly more effective than gentamicin plus cefotaxim. The inferior results of this combination was confirmed later by the studies of the European Organization for Research and Treatment of Cancer (82). The advantage of monotherapy, being easier to apply, the effectivity and low toxicity strengthed us to explore further the applicability of ceftazidime in febrile neutropenic patients. In the first study, we were forced to modify therapy in a small subgroup of patients with resistant Gram-positive infections. Consequently, in a second study we compared ceftazidime monotherapy with the combination of ceftazidime plus flucloxacillin in 100 febrile neutropenic patients in an attempt to increase the coverage against staphylococcal infections (79). Although there was a slightly better outcome for staphylococcal infections, the overall clinical and bacteriological cure rate was not improved by the combination. This was due partly to the occurrence of Gram-positive pathogens resistant to both ceftazidime and flucloxacillin, and partly to the increase of superinfections in the group treated with the combination. Moreover, more than 10% of the patients treated with flucloxacillin experienced a drug induced exanthematous rash. Comparing the cure rates of ceftazidime monotherapy to the results of combination therapy (Table 4), it

was evident that this approach was successful as initial empiric therapy. However these data required further clinical confirmation as many questions remained unanswered.

REFERENCES

1. Hersh EM, Bodey GP, Nies BA, Freireich EJ. Causes of death in acute leukemia. JAMA (1965) 193; 99-103.
2. Chang HY, Rodriguez V, Narboni G, et al. Causes of death in adults with acute leukemia. Medicine (1976) 55; 259-268.
3. Brown AE. Neutropenia, fever, and infection. Am. J. Med. (1984) 76; 421-428.
4. Bodey GP, Buckley M, Sathe YS, Freireich EJ. Quantitative relationships between circulating leukocytes and infection in patients with acute leukemia. Ann. Intern. Med. (1966) 64; 585-589.
5. Bodey GP. Infection in cancer patients a continuing association. Am. J. Med. (1986) 81 Suppl. 1A; 11-26.
6. Bodey GP, Bolivar R, Fainstein V. Infectious complications in leukemic patients. Sem. Hematology (1982) 19; 195-226.
7. Hersh EM, Whitecar JP, McCredie KB, et al. Chemotherapy, immunocompetence, immunosuppression and prognosis in acute leukemia. N. Engl. J. Med. (1971) 285; 1211-1216.
8. Thompson EN, Williams R. Bactericidal capacity of peripheral blood leukocytes in relation to bacterial infections in acute lymphoblastic leukemia in childhood. J. Clin. Microbiol. (1974) 27; 906-910.
9. Weiner RS, Bortin MM, Gale RP, et al. Interstitial pneumonitis after bone marrow transplantation, assessment of risk factors. Ann. Intern. Med. (1986) 104; 168-175.
10. Winston DJ, Gale RP, Meyer D, Young LS, and UCLA-BMTG. Infectious complications of human bone marrow transplantation. Medicine (1979) 58; 1-31.
11. Bolivar R, Kohl S, Pickering CK. Effect of antineoplastic drugs on antibody dependent cellular toxicity mediated by human leukocytes against herpes simplex virus infected target cells. Cancer (1980) 46; 155-156.
12. Katz DH. The allergic phenotype: Manifestation of "allergic breakthrough" and imbalance in normal "damping" of IgE antibody production. Immun. Rev. (1978) 41; 77-108.
13. Press OW, Ramsey PG, Larson EB, et al. Hickman catheter infections in patients with malignancies. Medicine (1984) 63; 189-200.
14. Schimpff SC, Young VM, Greene WH, et al. Origin of infection in acute nonlymphoblastic leukemia: significance of hospital acquisition of potential pathogens. Ann. Intern. med. (1972) 77; 707-714.
15. Lefrock JL, Ellis CA, Weinstein L. The impact of hospitalization on the aerobic fecal microflora. Am. J. Med. Sci. (1979) 277; 269-274.
16. Fainstein V, Rodriguez V, Tasch M, et al. Patterns of oropharyngeal and fecal flora in patients with acute leukemia. J. Inf. Dis. (1981) 144; 10-18.
17. Van der Waay D, Berghuis-de Vries JM, Lekkerkerk-van der Wees JEC. Colonization resistance of the digestive tract in convential and antibiotic-treated mice. J. Hyg. (1971) 69; 405-411.

18. Sleyfer DTh, Mulder MH, De Vries-Hosperen HG, et al. Infection prevention in granulocytopenic patients by selective decontamination of the digestive tract. Eur. J. Cancer (1980) 16; 859-869.
19. Duma RJ, Wainer JF, Dalton HP. Septicemias from intravenous infusions N. Eng. J. Med. (1971) 284; 257.
20. Curry CR, Quie PG. Fungal septicemia in patients receiving parenteral hyperalimentation N. Eng. J. Med. (1971) 285; 1221-1225.
21. Burnie JP. *Candida* and hands. J. Hosp. Inf. (1986) 8;1-4.
22. Wade JC, Schimpff SC, Newman KA, Wiernik PH. *Staphylococcus epidermidis* An increasing cause of infection in patients with granulocytopenia. Ann. Intern. Med. (1982) 97; 503-508.
23. Young VM, Meyers WF, Moody MR, Schimpff SC. The emergence of coryneform bacteria as a cause of nosocomial infections in compromised hosts. Am. J. Med. (1981) 70; 646-650.
24. Kilton LJ, Fossieck Jr. BE, Cohen MH, Parker RH. Bacteremia due to gram-positive cocci in patients with neoplastic disease. Am. J. Med. (1979) 66; 596-602.
25. Pizzo PA, Robichaud KJ, Gill FA, Witebsky FG. Empiric antibiotic and antifungal therapy for cancer patients with prolonged fever and granulocytopenia. Am. J. Med. (1972) 72; 101-110.
26. Gold JWM. Opportunistic fungal infections in patients with neoplastic disease. Am. J. Med. (1984) 76; 458-463.
27. Bodey GP. Fungal infection and fever of unknown origin in neutropenic patients. Am. J. Med (1986) 80 Suppl. 5C; 112-119.
28. Grady GF, Bennet AJE. Risk of posttransfusion hepatitis in the United States. A prospective cooperative study. J. Am. Med. Ass. (1972) 220; 692-695.
29. De Pauw BE, Janssen JThP, Vaissier P, Haanen C. Occurrence of herpes zoster varicella infections after completion of treatment for Hodgkin's disease. Neth. J. Med. (1983) 26; 301-303.
30. Wong KK, Hirsch MS. Herpes virus infections in patients with neoplastic disease. Diagnosis and therapy. Am. J. Med. (84) 76; 464-478.
31. Neiman PE, Reeves W, Ray G. A prospective analysis of interstitial pneumonia and opportunistic viral infections among recipients of allogeneic bone marrow grafts. J. Infect. Dis. (1977) 136; 754-767.
32. Winston DJ, Ho WG, Howell CL, et al. Cytomegalovirus infections associated with leukocyte transfusions. Ann. Intern. Med. (1980) 93; 671-675.
33. Wong B. Parasitic diseases in immunocompromised hosts. Am. J. Med. (1984). 76; 479-486.
34. Nauseef WM, Maki DG. A study of the value of simple protective isolation in patients with granulocytopenia. N. Engl. J. Med. (1981) 304; 448-453.
35. Rodriguez V, Bodey GP, Freireich EJ. Randomized trial protected environment-prophylactic antibiotics in 145 adults with acute leukemia. Medicine (1978) 57; 253-266.
36. Schimpff SC, Greene WH, Young VM. Infection prevention in acute nonlymphocytic leukemia. Laminar flow room reverse isolation with oral, nonabsorbable antibiotic profylaxis. Ann. Intern. Med. (1975) 82; 351-358.
37. Armstrong D. Protected environments are discomforting and expensive and do not offer meaningful protection. Am. J. Med. (1984) 76; 685-689.
38. Klastersky J. Prevention and therapy of infection in myelosuppressed patients. In: J. Klastersky and MJ Staquet (eds.): Medical complications in cancer patients. (1981) Raven press, New York; 245.

39. Van der Waay D. The colonization resistance of the digestive tract in man and animals. S155-161 In: TM Fliedner, H Heit, D Niethammer, and H Pfieger (eds): Clinical and experimental gnotobiotics (1979) Zbl. Bakt. Suppl., Gustav Fisher Verlag, Stuttgart-New York.
40. Shooter RA, Cooke EM, Gaya H,et al. Food and medicaments as possible sources of hospital strains of *Pseudomonas aeruginosa*. Lancet (1969) I; 1227-1229.
41. Remington JS, Schimpff SC. Please don't eat the salads. N. Engl. J. Med. (1981) 304; 433-435.
42. Estey E, Maksymiuk A, Smith T, et al. Infection prophylaxis in acute leukemia. Comparative effectiveness of sulfamethoxazole and trimethoprim, ketoconazole and the combination of the two. Arch. Intern. Med. (1984) 144; 1562-1568.
43. Wilson JM, Guiney DG. Failure of oral trimethoprim-sulfamethoxazole prophylaxis in acute leukemia. Isolation of resistant plasmids from strains of enterobacteriaceae causing bacteremia. N. Engl. Med. (1982) 306;16-20.
44. Murray BE, Rensimer ER, DuPont HL. Emergence of high-level trimethoprim resistance in fecal *Escherichia coli* during oral administration of trimethoprim or trimethoprim-sulfamethoxazole. N. Engl. J. Med. (1982) 306;130-135.
45. Wells CL, Podzorski RP, Peterson PK, et al. Incidence of trimethoprim-sulfamethoxazole-resistant enterobacteriaceae among transplant recipients. J. Infect. Dis. (1984) 150; 699-706.
46. Bow EJ, Louie TJ, Riben PD, et al. Randomized controlled trial comparing trimethoprim/sulfamethoxazole and trimethoprim for infection prophylaxis in hospitalized granulocytopenic patients. Am. J. Med. (1984) 76; 223-233.
47. Kramer BS, Pizzo PA, Robichaud KJ, et al. Role of serial microbiologic surveillance and clinical evaluation in the management of cancer patients with fever and neutropenia.. An. J. Med. (1982) 72; 561-568.
48. Hughes WT, Kuhn S, Chaudhary SRN, et al. Successful chemoprophylaxis for *Pneumocystes carinii* pneumonitis. N. Engl. J. Med. (1977) 29; 1419-1426.
49. Saral R, Burns WH, Laskin OL. Acyclovir prophylaxis of *Herpes simplex* virus infections. A randomized double-blind, controlled trial in bone marrow transplant recipients. N. Engl. J. Med. (1981) 305; 63-67.
50. Winston DJ, Ho WG, Gale RP. Prophylactic granulocyte transfusions during chemotherapy of acute nonlymphocytic leukemia. Ann. Intern. Med. (1981) 94; 616-622.
51. Young LS. Immunoprophylaxis and serotherapy of bacterial infections. Am. J. Med. (1984) 76; 664-671.
52. Sickles EA, Greene WH, Wiernik PH. Clinical presentation of infection in granulocytopenic patients. Arch. Intern. Med. (1975) 135; 715-719.
53. Aelony Y. The role of transbronchial biopsy for the diagnosis of diffuse pneumonias in immunocompromised marrow transplant recipients. Am. Rev. Resp. (1983) 127; 329-330
54. Pennington JE, Feldman NT. Pulmonary infiltrates and fever in patients with hematologic malignancy, assessment of transbronchial biopsy. Am. J. Med. (1977) 62; 581-587.
55. Springmeyer SC, Silvestri RC, Sale GE, et al. The role of transbronchial biopsy for the diagnosis of diffuse pneumonias in immunocompromised marrow transplant recipients. Am. Rev. Respir. Dis. (1982) 126; 763-765.
56. Degregorio MW, Lee WMF, Linker CA, et al. Fungal infections in patients with acute leukemia. Am. J. Med. (1982) 73; 543-548.

57. Klastersky J. Empiric treatment of infections in neutropenic patients with cancer. Rev. Infect. Dis. (1983) 5; S21-S31.
58. Pizzo PA, Ladisch S, Sinon RM, et al. Increasing incidence of gram-positive sepsis in cancer patients. Med. Ped. Oncol. (1978) 5; 241-244.
59. Gerson SL, Talbot GH, Hurwitz S, et al. Prolonged granulocytopenia: The major risk factor for invasive pulmonary aspergillosis in patients with acute leukemia. Ann. Intern. Med. (1984) 100; 345-351.
60. Gerson SL, Talbot GH, Hurwitz S, et al. Discriminant scorecard for diagnosis of invasive pulmonary aspergillosis in patients with acute leukemia. Am. J. Med. (85) 79; 57-64.
61. Middelman EL, Watanabe A, Kaizer H, Bodey GP. Antibiotic combinations for infections in neutropenic patients, evaluation of carbenicillin plus either cephalothin or kanamycin. Cancer (1972) 30; 573-579.
62. Bodey GP, Valdivieso M, Feld R, et al. Carbenicillin plus cephalothin or cefazolin as therapy for infections in neutropenic patients. Am. J. Med. Sci. (1977) 273; 309-318.
63. EORTC. Three antibiotic regimens in the treatment of infection in febrile granulocytopenic patients with cancer. J. Infect. Dis. (1978) 137; 14-29.
64. Bodey GP, Ketchel SJ, Rodriguez V. A randomized study of carbenicillin plus cefanandole or tobramycin in the treatment of febrile episodes in cancer patients. Am. J. Med. (1979) 67; 608-616.
65. Keating MJ, Bodey GP, Valdivieso M, Rodriguez V. A Randomized comparative trial of three aminoglycosides: comparison of continuous infusions of gentamicin, amikacin and sisomycin combined with carbenicillin in the treatment of infections in neutropenic patients with malignancies. Medicine (1979) 58; 159-170.
66. Wade JC, Schimpff SC, Newman KA, et al. Piperacillin or ticarcillin plus amikacin. A double blind prospective comparison of empiric antibiotic therapy for febrile granulocytopenic cancer patients. Am. J. Med. (1981) 71; 983-990.
67. Winston DJ, Ho WG, Young LS, et al. Piperacillin plus amikacin therapy v carbenicillin plus amikacin therapy in febrile, granulocytopenic patients. Arch. Intern. Med. (1982) 142; 1663-1667.
68. De Jongh CA, Wade JC, Schimpff SC, et al. Empiric antibiotic therapy for suspected infection in granulocytopenic cancer patients. A comparison between the combination of moxalactam plus amikacin and ticarcillin plus amikacin. Am. J. Med. (1982) 73; 89-96.
69. De Pauw BE, Kauw F, Muytjens H, et al. Randomized study of ceftazidine versus gentamicin plus cefotaxim for infections in severe granulocytopenic patients. J. Antimicrob. Chemother. (1983) 12 Suppl A; 93-99.
70. Fainstein V, Bodey GP, Elting L, et al. A randomized study of ceftazidime compared to ceftazidime and tobramycin for the treatment of infection in cancer patients. J. Antimicrob. Chemother. (1983) 12 Suppl. A; 101- 110.
71. Fainstein V, Bodey GP, Bolivar R, et al. Moxalactam plus ticarcillin or tobramycin for treatment of febrile episodes in neutropenic cancer patients. Arch. Intern. Med. (1984) 144; 1766-1770.
72. Donnelly JP, Marcus RE, Goldman JM, et al. Ceftazidime as first-line therapy for fever in acute leukaemia. J. Infection (1985) 11; 205-215.
73. Bezwoda WR, Derman DP, Perkins S, Cassel R. Treatment of neutropenic infection: a randomized trial comparing latamoxef (moxalactam) with cefradine plus tobramycin. J. Antimicrob. Chemother. (1985) 15; 239-245.

74. Winston DJ, Barnes RC, Ho WG, et al. Moxalactam plus piperacillin versus moxalactam plus amikacin in febrile granulocytopenic patients. Am. J. Med. (1984) 77; 442-450.
75. Feld R, Rachlis A, Tuffnell PG, et al. Empiric therapy for infections in patients with granulocytopenia, continuous versus interrupted infusion of tobramycin plus cefamandole. Arch. Intern. Med. (1984) 144; 1005-1010.
76. Jadeja L, Bolivar R, Fainstein V, et al. Piperacillin plus vancomycin in the therapy of febrile episodes in cancer patients. Antimicrob. Ag. Chemother. (1984) 26; 295-299.
77. Lawson RD, Gentry LO, Bodey GP, et al. A randomized study of tobramycin plus ticarcillin, tobramycin plus cephalothin and ticarcillin, or tobramycin plus mezlocillin in the treatment of infection in neutropenic patients with malignancies. Am. J. Med. Sci. (1984) 287; 16-23.
78. Williams ME, Harman C, Scheld M, et al. A controlled study of ticarcillin plus clavulanic acid versus piperacillin as empiric therapy for fever in the immunocompromised host. Am. J. Med. (1985) 79 Suppl. 5B; 67-72.
79. De Pauw B, Williams K, de Neeff J, et al. A randomized prospective study of ceftazidime versus ceftazidime plus flucloxacillin in the empiric treatment of febrile episodes in severely neutropenic patients. Antimicrob. Ag. Chemother. (1985) 28; 824-828.
80. Clough JV, Farrel ID, Wood MJ, Leyland MJ. Ceftazidime plus mezlocillin as initial antibiotic therapy in febrile neutropenic patients with haematological malignancy. J. Antimicrob. Chemother. (1985) 15; 353-363.
81. Jones PG, Rolston KVI, Fainstein V, et al. Aztreonam therapy in neutropenic patiens with cancer. Am. J. Med. (1986) 81; 243-248.
82. Klastersky J, Glauser MP, Schimpff SC, et al. Prospective randomized comparison of three antibiotic regimens for empirical therapy of suspected bacteremic infections in febrile granulocytopenic patients. Antimicrob. Ag. Chemother. (1986) 29; 263-270.
83. Pizzo PA, Hathorn JW, Hiemenz J. et al. A randomized trial comparing ceftazidime alone with combination antibiotic therapy in cancer patients with fever and neutropenia. N. Engl. J. Med. (1986) 315; 552-558.
84. Kraner BS, Ramphal R, Rand KH. Randomized comparison between two ceftazidime-containing regimens and cephalothin-gentamicin-carbenicillin in febrile granulocytopenic cancer patients. Antimicrob. Ag. Chemother. (1986) 30; 64-68.
85. Bodey GP, Alvarez ME, Jones PG, et al. Imipenem-cilastin as initial therapy for febrile cancer patients. Antimicrob. Ag. Chemother. (1986) 30; 211-214.
86. De Jongh CA, Joshi JH, Thompson BW, et al. A double beta-lactam combination versus an aminoglycoside-containing regimen as empiric antibiotic therapy for febrile granulocytopenic cancer patients. Am. J. Med. (1986) 80 Suppl. 5C; 101-111.
87. Piccart M, Klastersky J, Meunier F, et al. Single-drug versus combination empirical therapy for gram-negative bacterial infections in febrile cancer patients with and without granulocytopenia. Antimicrob. Ag. Chemother. (1984) 26; 870-875.
88. Love LJ, Schimpff SC, Hahn DM, et al. Randomized trial of empiric antibiotic therapy with ticarcillin in combination with gentamicin, amikacin or netilmicin in febrile patients with granulocytopenia and cancer. Am. J. Med. (1979) 66; 603-610.

89. Lau WK, Young LS, Black RE, et al. Comparative efficacy and toxicity of amikacin/carbenicillin versus gentamicin/carbenicillin in leukopenic patients. A randonized prospective trial. Am. J. Med. (1977) 62; 959-966.
90. Bodey GP, Middleman E, Umsawadi T, Rodriguez V. Infections in cancer patients. Results with gentamicin sulfate therapy. Cancer (1972) 29; 1697-1701.
91. Klastersky J, Henri A, Hensgens C, Daneau D. Empiric therapy for cancer patients: comparative study of ticarcillin-tobramycin, ticarcillin-cephalothin, and cephalothin-tobramycin. Antimicrob. Ag. Chemother. (1975) 7; 640-645.
92. Dejace P, Klastersky J. Comparative review of combination therapy: Two beta-lactams versus beta-lactam plus aminoglycoside. Am. J. Med. (1986) 80 Suppl. 6B; 29-38.
93. Sculier JP, and Klastersky J. Significance of serum bactericidal activity in gram-negative bacillary bacteremia in patients with and without granulocytopenia. Am. J. Med. (84) 76; 429-435.
94. Wood CA, Kohlhepp SJ, Kohnen PW, et al. Vancomycin enhancement of experimental tobramycin nephrotoxicity. Antimicrob. Ag. Chemother. (1986) 30; 20-24.
95. Whiting PH, Simpson IG, Thomson AW. Nephrotoxicity of cyclosporin in combination with aminoglycoside and cephalosporin antibiotics. Transplant Proc (1983) 15; 2702-2706.
96. Haas A, Anderson L, Lad T. The influence of aminoglycosides on the nephrotoxicity of cis-diaminodichloroplatinum in cancer patients. J. Infect. Dis. (1983) 147; 363.
97. Bodey GP. Antibiotics in patients with neutropenia. Arch. Intern. Med. (1984) 144; 1845-1851.
98. Rolinson GN. Beta-lactam antibiotics. J. Antimicrob. Chemoth. (1986) 17; 5-36.
99. Mead GM, Smith AG. Allergic skin reactions to piperacillin in patients with acute leukaemia. Lancet (1985) II; 499.
100. Pizzo PA, Robichaud KJ, Gill FA. Duration of empiric antibiotic therapy in granulocytopenic patients with cancer. Am. J. Med. (1979) 67; 194-200.
101. Commers JR, Pizzo PA. Empiric antifungal therapy in the management of the febrile granulocytopenic cancer patient. Ped. Infect. dis. (1983) 2; 56-61.
102. Tenney JH, Moody MR, Newman KA, et al. Adherent microorganisms on luminal surfaces of long-term intravenous cathethers. Importance of *Staphylococcus epidermidis* in patients with cancer. Arch. Intern. Med. (1986) 146; 1949-1954.
103. Donnelly JP, Cohen J, Marcus R, and Guest J. Bacteraemia and Hickman catheters. Lancet (1985) II; 48.
104. Neu HC. Relation of structural properties of beta-lactam antibiotics to antibacterial activity. Am. J. Med. (1985) 79 Suppl. 2A; 2-13.
105. Norris SM, Guenthner SH, Wenzel RP. Comparative activity of seven extended spectrum cephalosporins against Gram-negative bacilli from blood cultures. J. Antimicro. Chemother. (1985) 16; 183-188.
106. Richards DM, Brogden RN. Ceftazidime. A review of its antibacterial activity, pharmacokinetic properties and therapeutic use. Drugs (1985) 29; 105-161.

CHAPTER 2
OUTLINE OF INVESTIGATION

The aim of this thesis was to explore further the strong and weak aspects of ceftazidine monotherapy in the empiric treatment of febrile neutropenic patients.

Chapter 3: Gram-positive microorganisms are less susceptible for ceftazidime in vitro, than the earlier generation cephalosporins. It was noticed, that patients who failed on initial ceftazidime monotherapy due to infections by Gram-positive pathogens did well after additional therapy with cephalothin. Based on the favourable results achieved in these patients, we performed a prospective randomized study of ceftazidime plus cephalothin versus ceftazidime alone as empiric therapy in febrile neutropenic patients. The theoretically preferable combination of ceftazidime plus vancomycin could not be explored, because both were investigational drugs at that time in The Netherlands.

Chapter 4 The conventional formulation of ceftazidime is blended with sodiun carbonate in order to improve the solubility. On disolving this blend, the pressure in the vial may increase, expelling part of its contents and spreading a fishy odor. Moreover, the generated carbondioxide may form numerous small bubbles in the infusion lines. A new formulation, ceftazidime arginine which should lack these sequella was developed. In this chapter the results of comparing the effectivity and safety of both formulations in the empiric treatment of febrile neutropenic patients, are reported.

Chapter 5 Neither flucloxacillin, nor cephalothin did add substantially to the efficacy of ceftazidime when given in combination as empiric therapy for febrile neutropenic patients. Modification of therapy remained necessary in a minority of the patients. Vancomycin proved to be a reliable drug in case a failure due to Gram-positive infection did occur during previous studies. Therefore, teicoplanin, a new glycopeptide antibiotic, with theoretically less toxicity and practical advantages was assessed as rescue therapy for ceftazidime monotherapy in an open study; the results are described in this chapter.

Chapter 6 Early infectious death in the immunocompromised host is mainly associated with Gram-negative infections. Any empiric therapy in neutropenic patients must provide evidence of efficacy in Gram-negative infections; the bottle-neck has been mainly failures due to infections caused by *Pseudomonas aeruginosa*. In this chapter a retrospective study is reported, analyzing the effectivity of ceftazidime alone in case of bacteriologically documented ***Pseudomonas aeruginosa*** infections.

Chapter 7 Conventional combination therapy is associated with well known side effects. Among others, possible nephrotoxicity is a matter of concern in case of fever in bone marrow transplant patients, due to the interaction of cyclosporin-A and notably aminoglycosides. The consequences of the administration of ceftazidime for the kidney function of patients treated with cyclosporin-A after allogeneic bone marrow transplantation are reported in this study.

Chapter 8 The most frequently reported side effect of drugs is an allergic skin reaction. A higher incidence of drug associated toxicodermia has been found in some diseases. We explored the incidence of skin reactions due to cephalosporins and other drugs in patients suffering from acute non lymphocytic leukemia.

Chapter 9 Fever is the most reliable indication of infection in the neutropenic patient. Still subtle symptons of localized infections may be discovered on examination. Conventional combination therapy proved to be less effective when tissue invasion occurs. We reassessed all patients treated with ceftazidime alone during four studies in order to define the possible role of ceftazidime monotherapy in febrile neutopenic patients with a localized infection.

CHAPTER 3

A RANDOMIZED PROSPECTIVE STUDY OF CEFTAZIDIME VERSUS CEFTAZIDIME PLUS CEPHALOTHIN IN THE EMPIRIC TREATMENT OF FEBRILE EPISODES IN SEVERELY NEUTROPENIC PATIENTS. *

C. STANS VERHAGEN*, BEN DE PAUW*, THEO DE WITTE*, JOS JANSSEN*, KEITH WILLIAMS+, PIETER DE MULDER*+, THEO BOTHOF**.

* Division of Hematology, Department of Internal Medicine, University Hospital St Radboud, Nijmegen, The Netherlands
*+ Division of Oncology, Department of Internal Medicine, University Hospital St Radboud, Nijmegen, The Netherlands
** Glaxo B V , Nieuwegein, The Netherlands
\+ Glaxo Group Research Ltd, Greenford, United Kingdom

* **(Accepted : Antimicrobial Agents and Chemotherapy).**

SUMMARY

In a prospective, randomized study, ceftazidime monotherapy was compared with a combination of ceftazidime plus cephalothin in 102 febrile neutropenic patients. Thirty bacteriologically documented infections, of which 23 were bacteremias, in 40 clinically assessable patients were treated with ceftazidime alone. Twenty-four bacteriologically proven infections, of which 18 were bacteremias, in 42 clinically assessable patients were treated with a combination of ceftazidime and cephalothin. The clinical response rates in assessable patients were 77% for ceftazidime monotherapy and 88% for the combination. The bacteriological clearance rate was 70% for ceftazidime monotherapy and 79% for the combination. Efficacy against Gram-negative pathogens appeared to be excellent, with 93% clearance for ceftazidime monotherapy and 100% clearance for the combination. The bacteriological clearance of Gram-positive infections was only 60% for both arms, with failures mainly due to *Streptococcus faecalis* and *Streptococcus sanguis*, primarily resistant to both ceftazidime and cephalothin. After addition of vancomycin to those infections which did not respond to empiric therapy, bacteriological clearance rates of 94% (ceftazidime plus vancomycin) and 90% (ceftazidime and cephalothin plus vancomycin) were achieved. Three superinfections were registered in the ceftazidime group and two in the combination group. Other adverse events on ceftazidime were minimal and not enhanced by combination with cephalothin. It is concluded that ceftazidime is an effective drug for the empiric treatment of febrile neutropenic patients, especially if one is prepared to modify therapy if resistant Gram-positive strains or mycotic infections are encountered. Neither the clinical nor bacteriological cure rates could be substantially improved by adding cephalothin to ceftazidime in initial empiric treatment of febrile neutropenic patients.

INTRODUCTION

Despite substantial improvement in supportive care, infection remains the major cause of morbidity and mortality in patients with bone marrow failure secondary to malignant diseases or cytotoxic treatment. Early institution of empiric antibiotic therapy has become standard practice for the initial management of febrile episodes in neutropenic patients. Synergistic schedules comprising two or three drugs, including aminoglycosides have been used and early death due to inadequately treated bacterial infections has been largely overcome. However concern for nephrotoxicity and ototoxicity can limit the use of aminoglycoside containing schedules, especially in the growing group of patients treated concomitantly with other potentially nephrotoxic drugs such as amphotericin-B, cisplatinum, and cyclosporin-A. Ceftazidime, in view of its excellent Gram-negative spectrum in vitro (10,14), was shown to be comparable to the established aminoglycoside containing schedules in different studies as reviewed by Pizzo (11) and offers the opportunity of monotherapy in the febrile neutropenic patient.

We have previously assessed the role of ceftazidime as empiric monotherapy for febrile episodes in granulocytopenic patients in two randomized comparative trials. In the first study (3) ceftazidime was shown to be significantly superior to a combination of gentamicin and cefotaxime. Because of the lesser activity of ceftazidime against Gram-positive infections, we were forced to modify the initial ceftazidime monotherapy in a small subgroup of patients. In the second comparative trial (4) flucloxacillin in combination with ceftazidime did not improve the efficacy of ceftazidime monotherapy. This was partly due to Gram-positive organisms found to be initially resistant to both drugs, partly caused by emerging resistance to flucloxacillin, and to more superinfections in the group treated with the combination schedule. Patients who failed to respond to ceftazidime alone or to the combination with flucloxacillin were switched successfully to the combination of ceftazidime plus cephalothin. Hence, it was decided to compare a combination of ceftazidime plus cephalothin with ceftazidime alone prospectively. Furthermore it was not possible to evaluate the combination of vancomycin plus ceftazidime as both were investigational drugs in The Netherlands at that time. The actual study protocol was agreed by the local Ethical Committee.

PATIENTS AND METHODS

This study was performed at the division of Hematology and Oncology, University Hospital St. Radboud, Nijmegen, The Netherlands, from March 1984 to March 1985. All consecutive patients over 14 years of age with an absolute granulocyte count of less than 1,000/mm^3, who became clinically septicemic with a temperature of 38.5° C or more in the absence of an obvious non-infectious cause of fever were eligible for the study. Exclusion criteria were: a history of allergy to cephalosporins or systemic treatment with antibacterial agents in the previous 72 hours, except for oral co-trimoxazole as part of selective gut decontamination. All patients were nursed in reverse isolation and received prophylactically selective gut decontamination with co-trimoxazole, polymyxin-B and ketoconazole as previously described (4).

Pretreatment evaluation included a complete history, physical examination and cultures from the blood, urine, mouth, nose, throat, sputum, and any clinically suspicious lesion. Antimicrobial disc susceptibility testing was done according to the method of Kirby Bauer (2). Discs containing 30 mcg ceftazidime were used. Laboratory investigation included hemoglobin and hematocrit, thrombocyte count, leukocyte count and differential, serum creatinine, glutamic-oxaloacetic transaminase, glutamic-pyruvic transaminase and urinalysis which were performed as previously described (4).

After informed consent was obtained, the patients were randomly allocated to receive either ceftazidime alone (2 g intravenously every 8 hours) or a combination of ceftazidime (2 g intravenously every 8 hours) plus cephalothin (2 g intravenously every 6 hours), all as 30 minute infusions. When systemic therapy was started, selective gut decontamination was terminated except for the antifungal compound. The empiric therapy was evaluated at 72 hours and modified or substituted only if the patient had not responded, unless adverse reactions or isolation of a pathogen resistant to the antibiotic(s) administered in the presence of a deteriorating clinical status urged an earlier change in therapy. In general therapy was continued until the patient was free of symptoms of infection for 4 days or for 2 days in cases in which the granulocyte count had increased to at least 1000/mm^3.

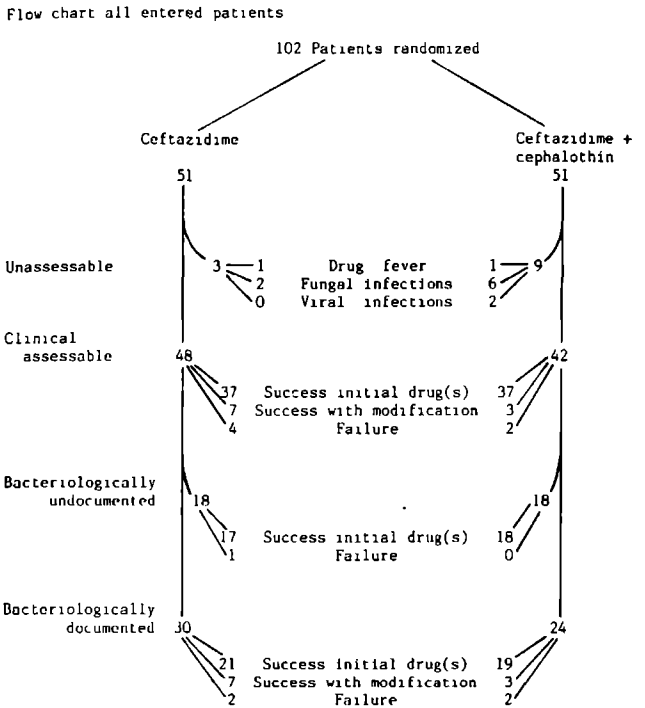
Clinical responses were classified as: (a) Success, if all clinical signs and symptoms subsided on the empiric regimen without evidence of infection or recrudescence of fever at the time the antibiotics were discontinued, nor during follow up; (b) Success with modification, if resolution of infection occurred only after addition of other agents to the empiric treatment regimen; (c) Failure, if there was no clinical response to initial therapy, even after treatment modification, and alternative therapy had to be given, or death occurred within 72 hours: (d) All those cases which proved to be viral or fungal infections, or when the protocol was violated, were classified as unassessable.

Microbiological responses were defined as: (a) Success, if the original causative organism was eradicated; (b) Success with modification, if the original causative organism could be eradicated only after modification ; (c) Failure if cultures remained positive; (d) Cases were bacteriologically unassessable for the same reasons as mentioned in the clinical definition supplemented by those for whom no organism could be isolated. Any infection occuring during treatment and not recognized as the initial causative organism was defined as a superinfection if further treatment was required. All new isolates without apparent signs of infection and not requiring treatment were defined as colonizations.

RESULTS

One-hundred and two patients were included in the study. Septicemia and bronchopneumonia proved to be the main infections. Underlying disease, degree of granulocytopenia, mean age, and weight were evenly matched in both study groups. The proportion of women was higher in the ceftazidime monotherapy group compared to the group with combination therapy, but the difference was not significant (Table 1). Fifty-one patients were allocated to both study arms. (See flow chart) Three patients in the ceftazidime group (2 fungal infections, 1 drug fever), and nine patients treated with cefazidime plus cephalothin (2 proven viral infections, 6 fungal infections, 1 drug fever), were unassessable for response. Details of the unassessable patients are summarized in Table 2.

The results of treatment are shown in Table 3 and 4. Initial empiric therapy was successful in keeping alive 96% of patients treated with



ceftazidime monotherapy, when evaluated after 72 hours of therapy. One patient with a positive blood culture of ***Escherichia coli*** was admitted in septic shock and died after only one dose of ceftazidime and one patient treated with ceftazidime monotherapy died on the third day due to *Candida* pneumonitis, confirmed at autopsy. For ceftazidime plus cephalothin the initial empiric therapy, evaluated at 72 hours, was successful in the prevention of early fatal outcome in 98% of the patients. One patient with gastric carcinoma and paralytic ileus developed a *Candida albicans* plus ***Escherichia coli*** septicemia and died on the third day of treatment due to persisting shock.

Although the data are not shown in the tables, ceftazidime as empiric monotherapy was successful in 72% of all cases (including assessable and unassessable patients) with a return of temperature and clinical conditions to normal; a further 14% responded to additional antibiotics, and 2% to antifungal agents. Thirty-seven out of 51 (72%) febrile episodes treated with ceftazidime plus cephalothin responded clinically, a further 6% responded after the addition of other antibacterials, and 6% after addition of antifungals.

Analysis of the assessable cases only showed that thirty-seven (77%) out of 48 patients were successfully treated with ceftazidime alone, and a further 15% responded to additional antibiotics. Ceftazidime plus cephalothin as empiric therapy was successful in 37 (88%) of 42 clinically assessable patients, and a further 7% responded to additional antibiotics.

TABLE 1

Clinical data on treated patients

Parameter	Treatment	
	Ceftazidime	Ceftazidime and Cephalothin
No. of patients (men/women)	51 (24/27)	51 (30/21)
Mean age (range) years	42 (14-78)	40 (15-74)
Underlying disease (No of patients)		
Acute leukemia	27	27
Myeloproliferative syndrome	6	7
Malignant lymphoma	6	5
Aplastic anemia	5	4
Solid tumors	7	8
(Of which patients with bone marrow transplantation)	(11)	(5)
No of patients with bacteriologically proven infections	31	28
Infection sites (No of patients)		
Fever of unknown origin	16	23
Septicemia	23	18
Upper respiratory tract	7	4
Lower respiratory tract	9	10
Skin and soft tissue	1	1
No of patients with two unique infection sites	5	5
No (%) of patients with granulocyte count at the start of treatment: $< 250/mm^3$	27 (53%)	25 (49%)
$250-500/mm^3$	17 (33%)	16 (31%)
$501-1000/mm^3$	7 (14%)	10 (20%)

TABLE 2

Non bacterial origin of fever and unassessable patients.

Origin of fever	Susceptibility	Rescue scheme	Outcome
Ceftazidime monotherapy			
1. Bronchopneumonia: Torulopsis glabrata	Resistant	Amphotericin-B	Success.
2. Bronchopneumonia: Candida albicans + Ps. aeruginosa	Resistant Susceptible	None -	Died on third day Autopsy confirmed C. albicans/ Ps. aeruginosa was eradicated.
3. Drug fever to earlier instituted cephalothin gargle. Subsided after withdrawl of the drug.			
Ceftazidime plus Cephalothin			
1. Bronchopneumonia Parainfluenza virus	Resistant	None	Success
2. Bronchopneumonia: Parainfluenza virus	Resistant	None	Success
3. Bronchopneumonia: Candida albicans + Escherichia coli	Resistant Susceptible	Miconazole None	Success Eradicated
4. Bronchopneumonia: Candida albicans + Bacteroides melanogenicus	Resistant Resistant	Miconazole Erythromycin	Died fifth day of onset without eradication.
5. Pharyngitis: Candida albicans + Septicemia: Proteus mirabilis + Staphylococcus epidermidis	Resistant Susceptible Susceptible	Miconazole None None	Success Eradicated Eradicated
6. Septicemia: Candida albicans	Resistant	Amphotericin-B	Success
7. Septicemia: Candida tropicalis	Resistant	Miconazole	Success
8. Septicemia: Candida albicans + Escherichia coli	Resistant Susceptible	None -	Died third day, persistant shock, no eradication.
9. Drug fever by anti thymocyte globulin treatment. Subsided after finishing ATG. course.			

TABLE 3

Results of therapy in assessable patients

Parameter	Treatment	
	Ceftazidime	Ceftazidime and Cephalothin
No of assessable patients	48	42
Days of therapy with ceftazidime (Mean ± Standard deviation: (range))	9.0 ± 5.0 (0.3–31)	8.7 ± 3.6 (1.5–23)
Clinical outcome No (%) of patients:		
Cure empiric therapy	37 (77%)	37 (88%)
Cure modified therapy	7 (15%)	3 (7%)
Failure	4 (8%)	2 (5%)
Bacteriological outcome in documented infections		
No (%) of patients:	30	24
Eradication	21 (70%)	19 (79%)
Eradication after modification	7 (23%)	3 (13%)
Failure	2 (7%)	2 (8%)
Bacteriological outcome in septicemia		
No (%) of patients:	23	18
Eradication	15 (65%)	15 (83%)
Eradication after modification	6 (26%)	2 (11%)
Failure	2 (9%)	1 (6%)
Clinical outcome in bacteriologically undocumented infecions No (%) of patients:	18	18
Eradication	17 (94%)	18 (100%)
Failure	1 (6%)	-
Granulocyte count (%) of patients at time of response*		
< 250/mm^3	20 (54%)	15 (40%)
250– 500/mm^3	13 (35%)	17 (46%)
501–1000/mm^3	4 (11%)	5 (14%)

* For successfully treated patients.

In the ceftazidime group 30 out of 48 assessable patients had bacteriologically documented infections; 21 (70%) out of 30 responded to monotherapy. One patient died due to myocardial infarction on the fourth day without signs of infection, or positive cultures at autopsy. Although it was a bacteriological success, this patient was regarded as a clinical failure. Seven patients responded to modification with vancomycin, all with infections due to Gram-positive organisms. And two were failures despite modification. Of 42 assessable patients treated with ceftazidime plus cephalothin, 24 had bacteriologically documented infections. Nineteen (79%) responded to the initial therapy and 3 after modification.

The bacteriological results, based on positive cultures obtained before treatment, are shown in Table 5. There were no differences between both study groups. Twelve out of 20 Gram-positive organisms were eradicated by ceftazidime alone and 8 out of 14 were eliminated by ceftazidime plus cephalothin. All but one Gram-negative organisms were eradicated by ceftazidime monotherapy and all by the combination therapy. A

TABLE 4

Clinical successes after modification and failures of therapy

Original isolate	(Superinfection)	Ceftazidime susceptibility (original/ superinfection)	Rescue scheme and outcome
Ceftazidime monotherapy			
Success after modification			
1. Strep. sanguis (blood)		Susceptible (persisting)	Vancomycin - eradicated
2. H. influenzae (sputum)	(S. aureus (blood))	Susceptible (eradicated) /intermediate	vancomycin - eradicated
3. S. aureus (soft tissue) + Strep. faecalis (soft tissue)	(S. epidermidis (blood))	Resistant resistant /resistant	Vancomycin - eradicated vancomycin - eradicated vancomycin - eradicated
4. S. epidermidis (blood)		Resistant	Vancomycin - eradicated
5. H. influenzae (sputum) + B-haemolytic Strep. (blood)		Susceptible (eradicated) Susceptible (persisting)	Vancomycin - eradicated
6. S. epidermidis		Resistant	Vancomycin - eradicated
7. Strep. faecalis		Resistant	Vancomycin - eradicated
Failure			
1. E. coli (blood)		Susceptible	Died after first dose
2. Strep. sanguis (blood) Recurrence Strep. sanguis		Susceptible Resistant	Vancomycin (died)
3. E. coli (sputum) + K. pneumoniae (sputum)		Susceptible (eradicated) Susceptible (eradicated)	Died on fourth day after myocardial infarction.
4. No pathogen isolated. Patient died (after initial improvement) due to massive gastro intestinal bleeding.			
Ceftazidime plus cephalothin			
Success after modification			
1. Strep. sanguis (blood)		Intermediate (persisting)	Vancomycin + ampicillin eradicated
2. Strep. sanguis (blood)	(C. albicans (sputum))	Susceptible (persisting) /resistant	Erythromycin + amikacin + vancomycin eradicated amphotericin-B eradicated
3. E. coli (peri-anal fistula) + Strep. faecalis (peri-anal fistula) + S. epidermidis (peri-anal fistula)		Susceptible (eradicated) resistant resistant	Ampicillin eradicated ampicillin eradicated
Failure			
1. S. aureus (blood) + B-haemolytic Streptococcus (blood)		Susceptible Susceptible	After initial improvement died due to ARDS.
2. Strep. faecalis (sputum)		Intermediate	Vancomycin. Died due to pulmonary haemorrhage.

bacteriological clearance was achieved in 25 out of 34 (74%) assessable initial isolates by ceftazidime alone. In 24 out of 30 (80%) cases the causative organisms were eradicated by ceftazidime plus cephalothin.

TABLE 5

Distribution of pathogens and results of therapy by pathogen

Organism*	Ceftazidime			Ceftazidime and Cephalothin		
	S	M	F	S	M	F
S. aureus	4	1		1		1
S. epidermidis	4	2		4		
Streptococcus group A	3	1		2		1
Streptococcus sanguis	1	1	1		2	
Streptococcus faecalis		2			1	1
Streptococcus viridans				1		
H. influenzae	5			2		
E. coli	1		1	5		
Klebsiella pneumoniae	2			5		
Acinetobacter species				1		
Pseudomonas aeruginosa	5			3		

S = success, M = success after modification, F = failure

* Unassessable cases are not included (summarized in Table 2).

Seventeen out of the 18 (94%) assessable, bacteriologically undocumented infections were cured with ceftazidime alone; one died due to massive gastrointestinal bleeding after initial improvement. All 18 (100%) assessable patients with bacteriologically undocumented infections responded to the combination therapy without modification.

At the time of response the majority of the successfully treated patients were still profoundly neutropenic (Table 3). Twenty (54%) patients had less than 250 granulocytes per mm^3, compared with 15 (40%) in the ceftazidime plus cephalothin group. None of the successfully treated patients showed an increase of the neutrophil count above 1000/mm^3.

During ceftazidime monotherapy, three superinfections were registered: one *Staphylococcus epidermidis*, one *Staphylococcus aureus* and one *Candida albicans*, all organisms resistant to ceftazidime. In two patients, who received ceftazidime plus cephalothin, superinfections with organisms resistant to both drugs occurred: one *Clostridium difficile* and one *Candida albicans*.

One patient, treated with ceftazidime alone, suffered from drug fever and a skin rash; while two more patients developed exanthema. One patient, treated with ceftazidime and cephalothin, showed a transient rise of glutamic-oxaloacetic and glutamic-pyruvic transaminases. None of the patients had any sign of nephrotoxicity as measured by serum creatinine levels or of ototoxicity. No local reactions to the drugs were seen.

DISCUSSION

The data from this study and others (3-6,12), show that ceftazidime alone or in combination with another antibacterial gives excellent coverage against Gram-negative infections in the immunocompromised host, a prerequisite for any empiric treatment in this patient group (11). Increase of granulocyte count, which is associated with a better outcome (1) was not an important factor in these results. If judged after 72 hours treatment, ceftazidime proved to be a safe drug for empiric treatment in the neutropenic patient, with a survival rate of 96%. Primarily resistant Gram-positive infections , mainly due to *Strep. sanguis* and *Strep. faecalis*, necessitated modification of therapy in both arms of the study without unacceptable mortality. A moderately better outcome for ***Staph. aureus*** and ***Staph. epidermidis*** was found in the combination arm without reaching statistical significance; Five out of 6 (83%) staphylococcal infections were cured by the combination, versus 8 out of eleven (73%) by ceftazidime alone ($p>0.1$ Chi square with Yates correction). No antagonism was seen with ceftazidime and cephalothin.

The outcome of modification with vancomycin was satisfactory in both arms. Inclusion of this more toxic drug in initial empiric treatment may have improved the results (13), but this policy would have been beneficial for less than 10% of the patients in this study. Furthermore no patients succumbed as a result of omission of vancomycin. So by modification, if required, after 72 hours we avoided unecessary administration of vancomycin to the majority of the patients.

Concern has been expressed about double beta-lactam therapy in the immunocompromised host, especially for inducing beta-lactamase and resistance of Gram-negative micro-organisms (15), or inducing resistance

against a beta-lactamase susceptible compound (7). Ceftazidime has proven to be a weak beta-lactamase inducer (9). Besides the numbers of infecting strains are usually low in neutropenic patients so it is less likely that stable derepressed mutants will be encountered. In this study there was no evidence of reduced susceptibility in the double beta-lactam combination against Gram-negative organisms. Neither in the previous study, in which cephalothin served as a rescue scheme for the treatment of infections caused by Gram-positive organisms resistant to ceftazidime (4), nor in this study was induction of resistance observed. The only failures were due to primarily resistant strains.

Toxicity of ceftazidime was minimal, according to the data from the literature (8); no aggravation of toxicity was seen in combination with cephalothin in this study.

In conclusion, combination of ceftazidime with an anti-staphylococcal penicillin (4), aminoglycoside (6), or cephalothin did not improve the results of ceftazidime alone. Ceftazidime seems to be a safe and effective drug for monotherapy in the immunocompromised host, offering the opportunity to avoid the aminoglycosides and their inherent nephrotoxicity and ototoxicity. However, using monotherapy one should be prepared to modify therapy in case resistant Gram-positive strains or mycotic infections are encountered.

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REFERENCES

1. Bodey, G.P., M. Buckley, and Y.S. Sathi. 1966. Quantitative relationship between circulating leukocytes and infection in patients with acute leukemia. Ann. Int. Med. 64:328-339.
2. Bauer, A., W. Kirby, T. Sherris. 1966. Antibiotic susceptibility testing by standardized single disc method. Amer. J. Clin. Pathol. 45: 493-496.
3. De Pauw, B.E., F. Kauw, H. Muytjens, K. J. Williams, and T. Bothof. 1983. Randomized study of ceftazidime versus gentamicin plus cefotaxime for infections in severe granulocytopenic patients. J. Antimicrob. Chemother. 12 (Suppl. A):93-99.
4. De Pauw, B.E., K. Williams, J. de Neeff, T. Bothof, T. de Witte, R. Holdrinet, and C. Haanen. 1985. A randomized prospective study of ceftazidime versus ceftazidime plus flucloxacillin in the empiric treatment of febrile episodes in severely neutropenic patients. Antimicrob. Agents Chemother. 28:824-828.
5. Donnelly, J.P., R.E. Marcus, J.M. Goldman, J. Cohen, A.M. Worsley, D. Catovsky, J.H. Darrell, S.V. Want, and D.A.G. Galton. 1985. Ceftazidime as first-line therapy for fever in acute leukaemia. J. Infection 11:205-215.
6. Fainstein, V., G.P. Bodey, L. Elting, R. Bolivar, M.J. Keating, K.B. McCredle, and M. Valdivieso. 1983. A randomized study of ceftazidime compared to ceftazidime and tobramycin for the treatment of infections in cancer patients. J. Antimicrob. Chemother. 12 (Suppl. A):101-110.
7. Fu, K.P., and H.C. Neu. 1981. The role of inducable beta-lactamases in the antagonism seen with certain cephalosporin combinations. J. Antimicrob. Chemother. 7:104-107.
8. Meyers, B.R. 1985. Comparative toxicities of the third-generation cephalosporins. Am. J. Med. 79 (Suppl. 2A):96-103.
9. Neu, H.C. 1985. Relation of structural properties of beta-lactam antibiotics to antibacterial activity. Am. J. Med. 79 (Suppl. 2A): 2-13.
10. Norris, S.M., S.H. Guenthner and R.P. Wenzel. 1985. Comparative activity of seven extended-spectrum cephalosporins against Gram-negative bacilli from blood cultures. J. Antimicrob. Chemother. 16: 183-188.
11. Pizzo, P.A., M. Thaler, J. Hathorn, J. Skelton, J. McKnight, M. Rubin, M. Browne, D. Longo, D. Cotton, J. Gress, D. Marshall. 1985. New beta-lactam antibiotics in granulocytopenic patients, new options and new questions. Am. J. Med. 79 (Suppl. 2A): 75-82.
12. Pizzo, P.A., J.W. Hathorn, J. Hiemenz, M. Browne, J. Commers, D. Cotton, J. Gress, D. Longo, D. Marshall, J. MacKnight, M. Rubin, J. Skelton, M. Thaler and R. Wesley. 1986. A randomized trial comparing ceftazidime alone with combination antibiotic therapy in cancer patients with fever and neutropenia. N. Engl. J. Med. 315: 552-558.
13. Ramphal, R., B.S. Kramer, K.H. Rand, and D. Peleir. 1984. A randomized comparison of ceftazidime (C) versus cephalothin, gentamicin, carbenicillin (KGC) versus ceftazidime plus vancomycin (CV) in febrile (F+) granulocytopenic (G+) cancer patients. In: program and Abstracts of the 24th Interscience Conference on Antimicrobial Agents and Chemotherapy. Washington: American Society for Microbiology: Nr. 378, P. 157.
14. Rolinson N. 1986. Beta-lactam antibiotics. J. Antimicrob. Chemother. 17:5-36.
15. Young, L.S. 1985. Double beta-lactam therapy in the immunocompromised host. J. Antimicrob. Chemother. 16:4-6.

CHAPTER 4

CEFTAZIDIME MONOTHERAPY AS EMPIRICAL TREATMENT IN FEBRILE NEUTROPENIC PATIENTS : A PROSPECTIVE RANDOMIZED STUDY OF CEFTAZIDIME SODIUM-CARBONATE VERSUS CEFTAZIDIME ARGININE FORMULATION. *

C. VERHAGEN*, B.E. DE PAUW*, T. DE WITTE*, R.S.G. HOLDRINET*, T.J. BOTHOF**, G. BROWN*+, K.J. WILLIAMS*+, W. DU BOIS R.N.+, T. RIJSEMUS R.N.*

* Department of Haematology, University Hospital St Radboud, Nijmegen, The Netherlands.
\+ Department of Oncology, University Hospital St Radboud, Nijmegen, The Netherlands
** Glaxo BV, Nieuwegein, The Netherlands
*+ Glaxo Group Research Ltd, Greenford, United Kingdom.

* **(Submitted : The Journal of Antimicrobial Chemotherapy).**

SUMMARY

We compared in a prospective randomized trial the efficacy and safety of ceftazidime sodium carbonate salt (CAZ-NA) to an arginine formulation of ceftazidime (CAZ-ARG) as empirical monotherapy in 100 febrile neutropenic patients. Dissolving CAZ-NA often causes an unpleasant fishy odour and bubbles in the infusion lines, due to the generation of carbon dioxide; CAZ-ARG lacks these undesirable features. The clinical cure rate for CAZ-NA was 91% and for CAZ-ARG 83%. Fourty-two infections could be confirmed bacteriologically. Bacteriological cure rates were 87% for CAZ-NA and 81% for CAZ-ARG respectively. Only one infection-related fatal outcome (CAZ-ARG; *Corynebacterium parvum*) occurred during the first 3 days of therapy. All failures of treatment in bacteriologically proven infections were in patients with Gram-positive infections. The nursing staff found CAZ-Arg considerably easier to handle than CAZ-NA. Adverse events were negligible in both arms. Ceftazidime was confirmed to be safe and effective as empirical monotherapy in febrile neutropenic patients. CAZ-ARG is as effective and as safe as CAZ-NA without the above mentioned side-effects.

INTRODUCTION

Therapeutic approaches to haematological and malignant diseases are becoming more aggresive and effective, and consequently an increasing number of patients will be at risk for infections. Early institution of empiric antibiotic therapy has become standard practice for the initial management of febrile episodes in neutropenic patients. Multiple empirical antibiotic regimens have been evaluated over the years and have demonstrated an overall efficacy rate of 65-75%. The main differences between these various regimens are the occurrence of side effects such as nephrotoxicity, ototoxicity, bleeding disorders and suppressive effect on the recovery of neutropenia (Bodey, et al, 1976; Fainstein, et al, 1984; Keating, et al, 1979; Winston, et al, 1982). With the development of beta-lactam antibiotics with an extended spectrum especially against Gram-negative organisms (Norris, Guenthner, & Wenzel, 1985; Rolinson, 1986) monotherapy became a possible new option in the empirical approach to the febrile neutropenic patient (Donnelly, et al, 1985; Fainstein, et al, 1983; Pizzo, et al, 1985; Pizzo, et al, 1986; Ramphal, et al, 1984). We have previously assessed the role of ceftazidime (CAZ) in this group of patients and found it to compare favourably with the established combination schedules (De Pauw, et al, 1983; De Pauw, et al, 1985a; De Pauw, et al, 1985b), offering the possibility to avoid antibiotic related toxicity (Meyers, 1985; Verhagen, et al, 1986).

The marketed formulation of ceftazidime sodium carbonate (CAZ-NA) however has a practical drawback: dissolving the powder causes a fishy odour and non-toxic bubbles of carbon dioxide in the infusion lines. Therefore a new formulation, ceftazidime arginine (CAZ-ARG), which lacks these properties was developed. We compared the efficacy and safety of both compounds in a prospective randomized study in the empiric treatment of 100 febrile neutropenic patients.

PATIENTS AND METHODS

This study was performed at the Division of Haematology, University Hospital St. Radboud, Nijmegen, The Netherlands, from March 1985 to Januari 1986. All consecutive patients over 14 years of age with an absolute granulocyte count of less than $1000/mm^3$, who became clinically septicaemic,

with a temperature of 38.5° C or more in the absence of an obvious non-infectious cause of fever, were eligible for the study. Exclusion criteria were: a history of allergy to cephalosporins or systemic treatment with antibacterial agents in the previous 72 hours, except for oral co-trimoxazole as part of selective gut decontamination.

All patients were nursed in reverse isolation and received prophylactically selective gut decontamination with co-trimoxazole, polymyxin-B and ketoconazole as previously described (De Pauw, et al, 1985). Pretreatment evaluation included a complete history, physical examination and cultures taken from the blood, urine, mouth, nose, throat, sputum, and any clinically suspicious lesion. Antimicrobial disc susceptibility testing was done according to the method of Kirby Bauer (Bauer, Kirby, & Sherris, 1966). Discs containing 30 mcg CAZ were used. Laboratory investigation included haemoglobin and haematocrit, thrombocyte count, leukocyte count and differential, serum creatinine, glutamic-oxaloacetic transaminase, glutamic-pyruvic transaminase and urinalysis which were performed as previously described (De Pauw, et al, 1985).

After informed consent was obtained, the patients were randomly allocated to receive either CAZ-NA or CAZ-ARG (both 2 g intravenously every 8 hours). When systemic therapy was started, selective gut decontamination was terminated except for the antifungal compound. The empiric therapy was evaluated at 72 hours and modified or substituted only if the patient had not responded, unless adverse reactions or isolation of a pathogen resistant to the antibiotic administered in the presence of a deteriorating clinical status necessitated an earlier change in therapy. Daily drug administration records were kept by the nursing staff attending the patients to document any difference in handling of both formulations of ceftazidime, and of local or general reactions to administration of the antibiotic. Adverse events were confirmed by the attending physician. In general, therapy was continued until the patient had been free of symptoms of infection for 4 days, or for 2 days in cases in which the granulocyte count had increased to at least 1000/mm^3.

Clinical responses were classified as: (a) Success, if all clinical signs and symptoms subsided on the empiric regimen without evidence of infection or recrudescence of fever at the time the antibiotics were discontinued, nor during follow up; (b) Success with modification, if resolution of infection occurred only after addition of other agents to the empiric treatment regimen; (c) Failure, if there was no clinical response to

initial therapy, even after treatment modification, and alternative therapy had to be given, or death occurred within 72 hours: (d) Unassessable, for those cases which proved to be viral or fungal infections, or when a major protocol violation occurred. Microbiological responses were defined as: (a) Success, if the original causative organism was eradicated; (b) Success with modification, if the original causative organism could be eradicated only after modification ; (c) Failure if cultures remained positive; (d) Cases were bacteriologically unassessable for the same reasons as mentioned in the clinical definition or if no organism could be isolated. Any infection occurring during treatment and not recognized as the initial causative organism was defined as a superinfection if further treatment was required. All new isolates without apparent signs of infection and not requiring treatment were defined as colonizations.

RESULTS

One-hundred patients were included in the study, 50 in each arm. Underlying disease, degree of granulocytopenia, mean age and patients of both sexes were evenly matched in both study groups (Table I). More patients with septicaemia were randomized to CAZ-ARG. Although localized infections were distributed equally between both study groups, more patients with lower respiratory tract infection were treated with CAZ-NA.
Seven patients in CAZ-NA group (5 fungal, 1 viral infection and 1 case of tuberculosis), and 4 patients treated with CAZ-ARG (2 fungal infections, 1 case of tuberculosis and 1 non-infectious related death), were unassessable for response. Details of the unassessable patients are summarized in Table II.

The results of treatment are shown in Table III with details in Tables IV and V. Initial empiric therapy was successful in keeping alive 98% of the patients treated with CAZ monotherapy, when evaluated after 72 hours of therapy. One patient died due to a massive gastro-intestinal bleeding, not related to his infection, which was already improving. The other patient was admitted in shock, due to *Corynebacterium parvum* septicaemia, and died before a second dose of antibiotics could be given. Both cases occurred in the CAZ-ARG group.

TABLE I

Clinical data

Parameter	Ceftazidime		
	Arginine	Sodium	Total
No. of patients (male/female)	50 (27/23)	50 (24/26)	100 (51/49)
Mean age (range) years	45.5 (16–72)	43.2 (18–69)	44.4 (16–72)
Underlying disease (No of patients)			
Acute leukaemia	38	36	74
Myeloproliferative syndrome	4	4	8
Malignant lymphoma	2	2	4
Aplastic anaemia	2	3	5
Solid tumors	4	5	9
(Of which patients with bone marrow transplantation)	(9)	(6)	(15)
No. of patients with bacteriologically proven infections	27	18	45
Infection sites (No of patients)			
Fever of unknown origin	22	25	47
Septicaemia (secondary)	23 (3)	15 (4)	38 (7)
Upper respiratory tract	4	1	5
Lower respiratory tract	2	13	15
Skin and soft tissue	3	1	4
Urinary tract	1	–	1
No of patients with two separate infection sites	2	1	3
No (%) of patients with granulocyte count at the start of treatment: $< 250/mm^3$	36 (72%)	36 (72%)	72 (72%)
$250–500/mm^3$	4 (8%)	5 (10%)	9 (9%)
$501–1000/mm^3$	9 (18%)	8 (16%)	17 (17%)
$>1000/mm^3$	1 (2%)	1 (2%)	2 (2%)

TABLE II

Unassessable patients.

Origin of fever	Susceptibility	Rescue scheme	Outcome
Ceftazidime arginine			
1. Septicaemia: *Staphylococcus epidermidis*	Susceptible		Died on third day, of GI bleeding, while signs of infection were improving
2. Acute miliary tuberculosis	Resistant	None	Died on twentieth day, postmortem diagnosis.
3. Bronchopneumonia: *Candida albicans*	Resistant	Amphotericin-B	Died on fifth day.
4. Bronchopneumonia: *Candida tropicalis*	Resistant	Amphotericin-B	Improved.
Ceftazidime sodium			
1. Pleuritis: *Coxsackie-B* virus (ARDS)	Resistant	Artificial respiration.	Improved
2. Bronchopneumonia: *Aspergillus fumigatus*	Resistant	None	Died fourteenth day. *Aspergillus* postmortem diagnosis.
3. Bronchopneumonia: *Aspergillus fumigatus*	Resistant	Amphotericin-B	Died on tenth day.
4. Bronchopneumonia: *Candida albicans*	Resistant	Miconazole	Died on eleventh day.
5. Bronchopneumonia: *Candida albicans*	Resistant	Miconazole	Improved
6. Bronchopneumonia: *Candida albicans* + *Escherichia coli*	Resistant Susceptible	Amphotericin-B	Died on eighth day after *Streptococcus faecalis* superinfection.
7. Bronchopneumonia: Tuberculosis	Resistant	Streptomycin, rifampicin, INH	Improved

TABLE III

Results of therapy in assessable patients

Parameter	Ceftazidime		
	Arginine	Sodium	Total
No of assessable patients	46	43	89
Days of therapy with ceftazidime (Mean ± Standard deviation: (range))	9.0 ± 5.0 (0.3–31)	8.7 ± 3.6 (1.5–23)	8.9 ± 4.3 (0.3–31)
Clinical outcome No (%) of patients:			
Cure empiric therapy	38 (83%)	39 (91%)	77 (87%)
Cure modified therapy	7 (15%)	4 (9%)	11 (12%)
Failure	1 (2%)	-	1 (1%)
Bacteriological outcome in documented infections No (%) of patients:	26	16	42
Eradication	21 (81%)*	14 (87%)	35 (83%)*
Eradication after modification	4 (15%)	2 (13%)	6 (14%)
Failure	1 (4%)	-	1 (3%)
Bacteriological outcome in septicaemia No (%) of patients:	21	14	35
Eradication	17 (81%)	12 (86%)	29 (86%)
Eradication after modification	3 (14%)	2 (14%)	5 (14%)
Failure	1 (5%)	-	
Clinical outcome in bacteriologically undocumented infecions No (%) of patients:	21	27	48
Cure empiric therapy	18 (86%)	25 (93%)	43 (90%)
Cure modified therapy	3 (14%)	2(7%)	5 (10%)
Granulocyte count (%) of patients at time of response**			
< 250/mm³	25 (66%)	28 (72%)	53 (69%)
250- 500/mm³	8 (21%)	8 (20%)	16 (21%)
501-1000/mm³	3 (8%)	1 (3%)	4 (5%)
>1000/mm³	2 (5%)	2 (5%)	4 (5%)

* Included one clinical unassessable patient.
** For successfully treated patients.

Overall CAZ monotherapy was successful in 77% of all cases (including assessable and unassessable patients) with a return of temperature and clinical conditions to normal; a further 12% responded to additional antibiotics and 2% to antifungal agents. No difference in overall results were observed between the sodium and arginine formulations.

Analysis of the assessable cases showed that 39 (91%) out of 43 patients were successfully treated with CAZ-NA alone, and the remainder responded to the modified therapy. CAZ-ARG monotherapy was successful in 38 (83%) out of 46 clinically assessable patients, and a further 15% responded to additional antibiotics.

Forty-two of the 89 assessable patients had bacteriologically documented infections; 35 (83%) of the 42 were cured by ceftazidime alone. Fourteen (87%) out of 16 allocated to treatment with CAZ-NA responded to

monotherapy: two patients, both with Staphylococci resistant to ceftazidime responded after additional treatment. Twenty-six patients with a bacteriologically proven infection were treated with CAZ-Arg; 21 (81%) were cured by monotherapy, and a further 15% responded to additional antibiotics (see Table V).

At the time of response the majority of the successfully treated patients were still profoundly neutropenic. Fifty-three (69%) patients had less than 250 granulocytes per mm^3, and 95% less than $1000/mm^3$. Both formulations of CAZ were comparable, and did not show any substantial increase of the granulocyte count before response.

TABLE IV

Clinical successes after modification and failures of therapy

Original isolate	(Superinfection)	Ceftazidime susceptibility (original/ superinfection)	Rescue scheme and outcome	
Ceftazidime arginine				
Success after modification				
1. *Staph. epidermidis* (sputum)		Resistant	Vancomycin	eradicated
2. *Clostridium perfringens* (blood) *Staph. aureus* (blood)		Resistant Susceptible (eradicated)	Penicillin-G + vancomycin	eradicated
3. *Staph. epidermidis* (blood) *Corynebact. parvum* (blood)		Resistant resistant	Vancomycin vancomycin	eradicated eradicated
4. *Strep. viridans* (throat) *Staph. epidermidis* (throat)	(*C. albicans* (sputum)	Susceptible (eradicated) resistant /resistant	Vancomycin Itraconazole	eradicated died 30th day
5. Cutaneous phlegmona, no organism isolated			Vancomycin	improved
6. Fever of unknown origin		-	Vancomycin	improved
7. Fever of unknown origin		-	improved only after recovery of granulocytes.	
Failure				
1. *Corynebacterium parvum* (blood)		Resistant	Died after first dose	
Ceftazidime sodium				
Success after modification				
1. *Staph. aureus* (blood)		Resistant	Vancomycin	eradicated
2. *Enterobacter cloacae* (blood) *Staph. epidermidis* (blood)		Susceptible (eradicated) resistant	Teicoplanin	eradicated
3. Bronchopneumonia: no organism isolated		-	Erythromycin	improved
4. Fever of unknown origin		-	Vancomycin.	improved

TABLE V

Distribution of pathogens and results of therapy by pathogen*

Organism	Ceftazidime arginine			Ceftazidime sodium		
	S	M	F	S	M	F
S. aureus	4			4	1	
S. epidermidis	6	3		1	1	
Streptococcus sanguis	3			-		
Streptococcus viridans	7			3		
Corynebacterium parvum	-	1	1			
Campylobacter species	-			2		
H. influenzae	1			-		
Klebsiella pneumoniae	1			-		
Klebsiella oxytoca	-			1		
Enterobacter cloacae	1			1		
Pseudomonas aeruginosa	1			2		
Clostridium perfringens	-	1		-		

S = success, M = success after modification, F = failure
* Unassessable cases are not included (summarized in Table II).

Four superinfections occurred during monotherapy. Two in both arms, one *Streptococcus faecalis*, and 1 *Staphylococcus epidermidis* in the group treated with CAZ-NA, and one *Strep. faecalis* plus 1 *Candida albicans* during CAZ-ARG treatment.

One of the patients treated by CAZ-NA developed a skin rash. Three patients in each arm showed a transient rise in glutamic-oxaloacetic and glutanic-pyruvic transaminases, with a rapid return to normal after the end of treatment. A positive direct Coombs test without evidence of haemolysis occurred in 2 patients treated with CAZ-NA and 1 with CAZ-ARG. None of the patients had any sign of ototoxicity nor of nephrotoxicity as measured by serum creatine levels. No local reactions to the drugs were seen. Reconstitution of CAZ-NA generated carbon-dioxide and preparation of the infusion set was more time consuming in order to avoid bubbles entering the line. At times part of the content of the the vials was expelled by the raised pressure, generating an offensive odour. The CAZ-ARG formulation was favoured by the nursing staff because it lacked these disadvantages and was considerably easier to handle.

DISCUSSION

The success (based on survival) of initial empiric monotherapy with CAZ, judged after the first 72 hours of treatment was 98 out of 100. Two patients died during the first three days: one died of massive gastro-intestinal haemorrhage and one of infection associated shock within a few hours after admission. None of the established combination schedules could have prevented the death of these two patients. All remaining assessable

patients were cured by CAZ alone (87%) or after modification of therapy (12%).

Although Gram-positive infections are increasing in neutropenic patients (Wade, et al, 1982), Gram-negative microorganisms are associated with the highest mortality and failure rate, even in patients treated with an adequate antibiotic regimen (Bodey, Bolivar, & Fainstein, 1982; Klastersky, et al, 1986). No patient with a bacteriologically proven Gram-negative infection failed to respond to CAZ in this study. Failures in the assessable patients were all due to Gram-positive infections and one due to an anaerobic pathogen, which is in accordance with in vitro studies (Norris, 1985), though it is important to note that 82% of all Gram-positive microorganisms were eradicated by CAZ alone, and all initial failures responded to modification of therapy.

Of concern is the increasing group of patients affected with mycotic infections of the lower and upper respiratory tract. Only 2 (29%) out of seven patients with a mycotic bronchopneumonia survived in this study, despite systemic antimycotic therapy. More active antifungal agents will be needed to cure effectively systemic mycotic infections.

CAZ-ARG was as effective as CAZ-MA in this study. Side effects were minimal, equal in both groups, and restricted to transient mild elevation of liver transaminases in 6% of the patients. This did not interfere with the therapy. CAZ-ARG was preferred by the nurses, who found it to be much easier to handle and less time consuming in preparation.

An increase in granulocytes is known to be associated with a better outcome (Bodey, Buckley, & Sathi, 1966). In this study, 69% of the patients were still severely neutropenic, with granulocytes less than 250/mm^3 at the time of response. Only 5% showed an increase over 1000/mm^3, so this will not have been an important factor in the favourable results achieved.

Vigilance is required when monotherapy is used. Since CAZ was introduced in our clinic, five years ago, it has been used as monotherapy in over 350 neutropenic patients, and no change in antibiotic susceptibility has been observed in the major pathogens affecting these patients. Ceftazidime has proven to be a weak beta-lactamase inducer (Neu, 1985). Moreover, even an small inoculum of organisms at the infection site tend to systemic reactions in neutropenic patients (Sickles, Greene, & Wiernik, 1975). Early intervention with antimicrobial therapy , may prohibit the acquisition of stable derepressed mutants. Neither in this nor previous studies has induction of resistance been observed, the only

failures being due to primarily resistant strains.

In conclusion, CAZ monotherapy is effective and safe for the empirical treatment of the febrile neutropenic patient. Ceftazidime arginine formulation is as effective and safe as the ceftazidime sodium formulation without the production of the fishy smell and carbon dioxide bubbles.

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REFERENCES

Bauer A., Kirby W., Sherris T. (1966) Antibiotic susceptibility testing by standardized single disc method. American Journal of Clinical Pathology 45, 493-496.

Bodey G.P., Buckley M., and Sathi Y.S. (1966) Quantitative relationship between circulating leukocytes and infection in patients with acute leukemia. Annals of Internal Medecine 64, 328-339.

Bodey G.P., Rodriguez V., Valdivieso M., and Feld R. (1976) Amikacin for treatment of infections in patients with malignant diseases. Journal of Infectious Diseases 134: s421-s427.

Bodey G.P., Bolivar R., Fainstein V. (1982) Infectious complications in leukemic patients. Seminars in Hematology 19, 193-226.

De Pauw B.E., Kauw F., Muytjens H., Williams K.J., and Bothof T. (1983) Randomized study of ceftazidime versus gentamicin plus cefotaxime for infections in severe granulocytopenic patients. Journal of Antimicrobial Chemotherapy 12 (Suppl. A), 93-99.

De Pauw B.E., Williams K., De Neeff J., Bothof T., De Witte T., Holdrinet R., and Haanen C. (1985a) A randomized prospective study of ceftazidime versus ceftazidime plus flucloxacillin in the empiric treatment of febrile episodes in severely neutropenic patients. Antimicrobial Agents and Chemotherapy 28, 824-828.

De Pauw B.E., Bothof T., Williams K., Holdrinet R., and De Witte T. (1985b) A randomized study of ceftazidime versus ceftazidime plus cephalothin in febrile neutropenic patients. 14th International Congres on Chemotherapy Kyoto S. P52 abstr. 54.

Donnelly J.P., Marcus R.E., Goldman J.M., Cohen J., Morsley A.M., Catovsky D., Darrell J.M., Want S.V., and Galton D.A.G. (1985) Ceftazidime as first-line therapy for fever in acute leukaemia. Journal of Infection 11, 205-215.

Fainstein V., Bodey G.P., Elting L., Bolivar R., Keating M.J., McCredle K.B., and M. Valdivieso. (1983) A randomized study of ceftazidime compared to ceftazidime and tobramycin for the treatment of infections in cancer patients. Journal of Antimicrobial Chemotherapy 12 (Suppl. A), 101-110.

Fainstein V., Bodey G.P., Bolivar R., et al. (1984) Moxalactam plus ticarcillin or tobramycin for treatment of febrile episodes in neutropenic cancer patients. Archives of Internal Medicine 144, 1766-1770.

Keating M.J., Bodey G.P., Valdivieso M., and Rodriguez V. (1979) A randomized comparative trial of three aminoglycosides comparison of continous infusions of gentamicin, amikacin and sisomycin combined with carbenicillin in the treatment of infections in neutropenic patients with malignancies. Medicine 58, 159-170.

Klastersky J., Glauser M.P., Schimpff S.C., Zinner S.H., Gaya H., EORTC. (1986) Prospective randomized comparison of three antibiotic regimens for empirical therapy of suspected bacteremic infections in febrile granulocytopenic patients. Antinicrobial Agents and Chemotherapy 29, 263-270.

Meyers B.R. (1985) Comparative toxicities of the third-generation cephalosporins. American Journal of Medicine 79 (Suppl. 2A), 96-103.

Neu H.C. (1985) Relation of structural properties of beta-lactam antibiotics to antibacterial activity. American Journal of Medicine 79 (Suppl. 2A), 2-13.

Norris S.M., Guenthner S.H., and Wenzel R.P. (1985) Comparative activity of seven extended-spectrum cephalosporins against Gram- negative bacilli from blood cultures. Journal of Antimicrobial Chemotherapy 16, 183-188.

Pizzo P.A., Thaler M., Hathorn J., Skelton J., McKnight J., Rubin M., Browne M., Longo D., Cotton D., Gress J., Marshall D. (1985) New beta-lactam antibiotics in granulocytopenic patients, new options and new questions. American Journal of Medicine 79 (Suppl. 2A), 75-82.

Pizzo P.A., Hathorn J.W., Hiemenz J., Browne M., Commers J., Cotton D., Gress J., Longo D., Marshall D., McKnight J., Rubin M., Skelton J., Thaler M., and Wesley R. (1986) A randomized trial comparing ceftazidime alone with conbination antibiotic therapy in cancer patients with fever and neutropenia. New England Journal of Medicine 315, 552-558.

Ramphal R., Kraner B.S., Rand K.H., and Peleir D. (1984) A randomized comparison of ceftazidime (C) versus cephalothin, gentamicin, carbenicillin (KGC) versus ceftazidime plus vancomycin (CV) in febrile (F+) granulocytopenic (G+) cancer patients. In: program and Abstracts of the 24th Interscience Conference on Antimicrobial Agents and Chemotherapy. Washington: American Society for Microbiology: Nr. 378, P. 157.

Rolinson N. (1986) Beta-lactam antibiotics. Journal of Antimicrobial Chemotherapy 17, 5-36.

Sickles E.A., Greene W.H., and Wiernik P.H. (1975) Clinical presentation of infection in granulocytopenic patients. Archives of Internal Medicine 135, 715-719.

Verhagen C., De Pauw B.E., De Witte T., Holdrinet R.S.G., Janssen J.Th.P., Williams K.J. (1986) Ceftazidime does not enhance cyclosporin-A nephrotoxicity in febrile bone marrow transplantation patients. Blut 53, 333-339.

Wade J.C., Schimpff S.C., Newman K.A., and Wiernik P.H. (1982) *Staphylococcus epidermidis*: An increasing cause of infection in patients with granulocytopenia. Annals of Internal Medicine 97, 503-508.

Winston D.J., Ho W.G., Young L.S., Hewitt W.L., Gale R.P. (1982) Piperacillin plus amikacin therapy v carbenicillin plus amikacin therapy in febrile granulocytopenic patients. Archives of Internal Medicine 142, 1663-1667.

CHAPTER 5

TEICOPLANIN FOR THERAPY OF GRAM-POSITIVE INFECTIONS IN NEUTROPENIC PATIENTS. *

VERHAGEN C. and de Pauw B.E.

Division of Haematology, Department of Internal Medicine, University Hospital St Radboud, Nijmegen, The Netherlands

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SUMMARY

Teicoplanin was evaluated in 20 febrile neutropenic patients as additional treatment for suspected Gram-positive infections after inadequate response to initial empiric therapy with ceftazidime monotherapy. Five patients with primary septicaemia, 3 with secondary septicaemia, 12 with localized infections and 3 patients with pyrexia of unknown origin were treated with teicoplanin (200 mg bolus iv injection once daily after 400 mg loading dose), whilst ceftazidime (2g 8 hourly 30 min. infusions) was continued. Four patients were unassessable (tbc, viral infection, protocol violation, and non infectious pyrexial episode). Clinical cure for the combination was achieved in 11 of 16 assessable cases (69%). Ten of 11 (91%) bacteriologically confirmed infections were cured after addition of teicoplanin. Three strains of *Staphylococcus aureus*, 4 strains of *Staph. epidermidis* (of which 2 were methicillin resistant), and 3 strains of *Streptococcus faecalis* were isolated from successfully treated patients. One patient with *Aerococcus* and *Enterobacter cloacae* infection only improved after addition of erythromycin. One superinfection occurred with signs of interstitial pneumonitis in a patient following bone marrow transplantation. Neither ototoxicity nor nephrotoxicity occurred during treatment. Transient rise of liver transaminases was observed in 4 patients, but was attributable to teicoplanin in only one case.

We conclude that teicoplanin is a potentially effective and well tolerated antimicrobial agent in neutropenic patients with infections due to Gram-positive organisms.

INTRODUCTION

Early instituted empiric broad-spectrum antibiotic therapy has markedly reduced the morbidity and mortality from infections complicating neutropenia in patients treated for haematological and other malignancies.

Ceftazidime as empiric monotherapy has proven to be comparable with the established combination schedules (1-4), offering the possibility to avoid related toxicity (5-8). Like most combinations, ceftazidine has restricted activity against Gram-positive microorganisms, and in particular has no activity against methicillin resistant staphylococci and Gram-positive enterococci (9). Although usually less life-threatening than Gram-negative infections (10,11), the increase of multiresistant Gram-positive microorganisms in patients with neutropenia (12) has urged the search for potent antimicrobials covering these pathogens. No substantial improvement was found in two prospective studies comparing combination therapy of flucloxacillin (13) or cephalothin (14) plus ceftazidime with ceftazidine alone in the empiric treatment of febrile neutropenic patients. Failures in aproximatly 50% of all Gram-positive infections were mainly due to methicillin resistant staphylococci, some non haemolytic streptococci and Gram-positve enterococci. These patients were favourably treated with vancomycin.

Teicoplanin is a new glycopeptide antibiotic resembling the vancomycin-ristocetin group (15-17). Its spectrum is restricted to aerobic and anaerobic Gram-positive microorganisms (18). In vitro activity of teicoplanin resembles that of vancomycin for staphylococci, but is more active against streptococci and enterococci (19). Moreover, the very long half-live of teicoplanin, in excess of 40 hours (20), permits once daily administration. A suggested wider margin between toxic and therapeutic range in the animal model (21) needs confirmation in clinical studies, but may offer an alternative for the well known nephrotoxicity and ototoxicity of vancomycin (22,23). In vitro study of the activity of teicoplanin against clinical isolates of cancer patients was comparable to that of vancomycin (24). In addition, teicoplanin was shown to be effective and well-tolerated in Gram-positive infections in patients with various underlying diseases (25).

The present open study was designed to determine the efficacy and safety of teicoplanin in febrile neutropenic patients with suspected or proven Gram-positive infections, and who were not improving on empirically instituted ceftazidime monotherapy.

PATIENTS AND METHODS

This study was performed at the department of Haematology, St. Radboud University Hospital, Nijmegen, The Netherlands. All febrile neutropenic patients not improving on empirically instituted ceftazidime monotherapy after 48-72 hours, or with a superinfection due to a Gram-positive pathogen susceptible for teicoplanin, were eligible for this open study. Inclusion criteria for ceftazidime monotherapy and grounds for modification have been described previously (13). Those patients with a proven infection caused by other than Gram-positive microorganisms or pyrexia of non-infectious origin were excluded from this study. Also excluded were patients with a history of allergy to vancomycin (26), patients with renal insufficiency (creatinine clearance <30 ml/min.), or hepatic failure.

All patients were nursed in reverse isolation. Pretreatment evaluation included a complete history, physical examination and cultures from the blood, urine, mouth, nose, throat, sputum, and any clinically suspicious focus. Antimicrobial disc susceptibility testing was done according to the method of Kirby Bauer (27). Discs containing 30 mcg ceftazidime and 30 mcg teicoplanin were used. A zone of inhibition 14 mm was accepted as susceptible (28). Laboratory investigation included haemoglobin and haematocrit, thrombocyte count, leukocyte count and differential, serum creatinine, glutamic-oxaloacetic transaminase, glutamic-pyruvic transaminase alkaline phosphatase and bilirubin. Urinalysis included 24 hr creatinine excretion, protein, glucose content and microscopic examination.

After informed consent was obtained, teicoplanin (200 mg) dissolved in sterile water (3 ml) was administered as a slow bolus intravenous injection once daily after an initial loading dose of 400 mg. Ceftazidime (2 g intravenously every 8 hours) was continued, and also ketoconzole (200 mg once daily orally) or amphotericin-B (400 mg 6 hourly orally) for prevention of fungal colonisation. Therapy was usually continued until the patient was free of symptoms of infection for 4 days or for 2 days in cases in which the granulocyte count had increased to at least $1000/mm^3$.

Clinical responses were classified as:

(a) Success, if all clinical signs and symptons of the principal infection subsided without relapse during a follow up period of at least 4 weeks.

(b) Failure, if there was no clinical response to the combination teicoplanin plus ceftazidime and alternative therapy had to be given,

or death occurred after at least 48 hours treatment.

(c) Cases which later proved to be caused by viral or fungal infections, or when the protocol was violated, were classified as unassessable.

Microbiological responses were defined as:

(a) Success, if the original causative organism was eradicated

(b) Failure if cultures remained positive.

(c) Cases were bacteriologically unassessable if no Gram-positive pathogen was isolated or if there was a protocol violation.

Any infection occurring during treatment which was not due to the initial causative organism was defined as a superinfection if further treatment was required. All new isolates without apparent signs of infection and not requiring treatment were defined as colonization.

The concentrations of teicoplanin were measured in serum samples obtained 1 hr. after administration (peak) and immediately before the next dose (through). These measurements were performed on day 1, 2, 4, 7, 10, 14 and repeated once weekly thereafter. Levels were determined by the standard agar well diffusion method, using Bacto Antibiotic Medium Nr. 5 (Difco), with *Bacillus subtilis* Middlebrook spore suspension ($1/2 \times 10^4$ CFU), as the test organism. The assay detection limit was 2 mg L^{-1}.

Evaluation of the safety of teicoplanin included repetition of the laboratory tests twice weekly during and one week after discontinuation of treatment, as performed on initiation of therapy. Further cultures were obtained during treatment and follow-up period as clinically indicated and if suitable specimens were available. Potential ototoxicity was assessed by audionetry on the first day of treatment and was repeated once weekly during therapy and at follow-up.

RESULTS

Twenty patients, 14 men and 6 women, were included in the study. Septicaemia and bronchopneumonia proved to be the main infections. Acute leukaemia was the underlying disease in 13 patients, a myelodysplastic syndrome in 6, and aplastic anaemia in one other. Full details are given in table I.

One patient with a *Coxsackie-B* virus infection and one patient with a *Streptococcus mitis* septicaemia already improving on ceftazidime monotherapy, were unassessable for teicoplanin. (Both recovered

TABLE I

Clinical data on treated patients.

Parameter	
No. of patients (men/women)	20 (14/6)
Mean age ± SD (range) years	45.9 ± 17.4 (16)
Underlying disease No. of patients:	
Acute leukaemia	13 (65%)
Myeloproliferative syndrome	6 (30%)
Aplastic anaemia	1 (5%)
Infection sites No of patients	
Fever of unknown origin	3 (15%)
Septicaemia	5 (25%)
Upper respiratory tract infection	1 (5%)
Lower respiratory tract infection	6 (30%)
Soft tissue infection	3 (15%)
Urinary tract infection	2 (10%)
(Secondary septicaemia)	(4 20%)
No of patients with bacteriologically proven infections	13 (65%)
No (%) of patients with granulocyte count at the start of treatment $< 250/mm^3$	9 (45%)
$250-500/mm^3$	4 (20%)
$501-1000/mm^3$	2 (10%)
$>1000/mm^3$	5 (25%)

successfully) One patient with a combined mycotic and tuberculous bronchopneumonia and one patient with a haemhorragic pericarditis without obvious infection subsequently died. Both were considered unassessable.

The results of treatment are shown in table II with full details in Table III and IV. Clinical cure was achieved in eleven of 16 assessable cases (69%). Two patients with *Staphylococcus epidermidis* septicaemia showed an initial improvement with lowering of the temperature and eradication of the pathogens. But both suffered recurrence of fever and despite modification of treatment only improved after recurrence of the granulocytes. Although bacteriological successes, both were considered to be clinical failures. One patient with bronchopneumonia and negative cultures only improved after addition of erythromycin and was suspected to have a *Legionella pneumophilia* infection. Two patients with soft tissue infections only improved after modification of therapy. (see table III)
Ten out of 11 (91%) bacteriologically confirmed infections were cured after

Table II

Overall results of modified therapy.

Parameter		Results
No of assessable patients		16
Days pretreated with ceftazidime (Mean ± SD (range))		3.7 ± 2.1 (1- 9)
Days of therapy with teicoplanin*		9.6 ± 3.1 (6-17)
Duration of fever after start teicoplanin (days)*		2.7 ± 1.5 (1- 6)
Duration of symptoms after start teicoplanin (days)*		3.9 ± 2.2 (1- 8)
Clinical outcome No (%) of patients:	Cure	11 (69%)
	Failure	5 (31%)
Bacteriological outcome in documented infections No (%) of patients	Assessable	11
	Eradicated	10 (91%)
	Failure	1 (9%)
Granulocyte count (/) of patients at time of response*	< 250/mm³	4 (36%)
	250- 500/mm³	-
	501-1000/mm³	3 (28%)
	>1000/mm³	4 (36%)

* For successfully treated patients.

addition of teicoplanin. Three patients with persistent ***Staphylococcus aureus*** septicaemia (one resistant to ceftazidime and 1 secondary to a bronchopneumonia). Four patients had ***Staph. epidermidis*** infection, of which 2 were methicillin resistant. Three patients with ***Streptococcus faecalis*** infections, all of which were resistant to ceftazidime, were cured (See Table IV). The only bacteriologically proven infection assed as a failure was a patient with an ***Enterobacter cloacae*** cultured from a localized skin infection plus ***Aerococcus*** septicaemia which only responded to ampicillin plus erythromycin.

One superinfection occurred in a patient with chronic graft-versus-host disease after bone marrow transplantation, together with signs of interstitial pneumonitis, was considered possibly due to a Cytomegalovirus infection.

No nephrotoxicity was observed. The mean serum creatinine concentration before treatment was 86.3 umol/L, the mean highest value

Table III

Clinical and bacteriological features of patients who failed on teicoplanin therapy

Case no	Age (yr)	Infection	Organism	Susceptibility Teicoplanin	Susceptibility Ceftazidime	Rescue scheme and outcome
1.	18	Cellulitis + septicaemia	*Enterobacter cloacae* *Aerococcus*	Susceptible Susceptible	Susceptible Susceptible	Erythromycin–eradicated Ampicillin–eradicated
2.	66	Bronchopneumonia	No pathogen isolated	–	–	Erythromycin–improved
3.	66	Bronchopneumonia septicaemia	No pathogen isolated *Staph. epidermidis*	– Susceptible	– Resistant	Improved after rise in granulocytes Eradicated by teicoplanin
4.	19	Septicaemia	*Staph. epidermidis*	Susceptible	Susceptible	Eradicated by the combination, but second period of fever improved only after rise in granulocytes
5.	32	Cellulitis	No organism isolated	–	–	Metronidazole plus granulocyte transfusions–improved

observed during treatment was 83.8 uMol/L and 80.8 uMol/L during follow-up. Creatinine clearance was also apparently unaffected the mean values being: 106 ml/min. before treatment, lowest mean value 104 ml/min. during treatment, and 113 ml/min. during follow-up. No proteinuria or glucosuria occurred and no abnormalities were found in urinary sediments during treatment.

Table IV

Isolated pathogens of successfully treated patients

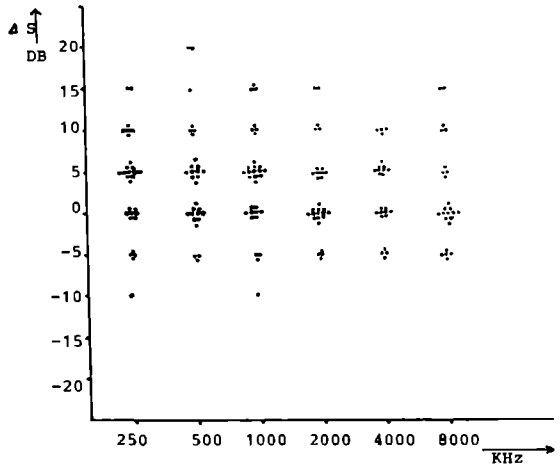
Case no.	Microorganism	Susceptibility Teicoplanin	Ceftazidime	Penicillin	Methicillin
1.	*Staphylococcus aureus*	+	+	not done	+
2.	*Staphylococcus aureus*	+	resistant	+	+
3.	*Staphylococcus aureus*	+	+	+	+
4–5.	*Staph. epidermidis*	+	+	+	+
6–7.	*Staph. epidermidis*	+	resistant	resistant	resistant
8–10.	*Streptococcus faecalis**	+	resistant	not done	not done

* Susceptible for ampicillin.

One of the patients complained of a right sided hearing loss after finishing an eleven days course of teicoplanin, however further examination showed an otitis serosa and his hearing was restored after decongestant

nose drops. Figure 1 shows a scatterdiagram of all changes in hearing sensitivity (ΔS) between audiograms performed before treatment and during follow-up. The mean change was an improvement of hearing sensitivity of ΔS 2-4 DB. None of the patients showed a consistant hearing loss. Four patients showed a transient 3-7 fold rise of glutamic-oxaloacetic transaminase and glutamic-pyruvic transaminase. Most likely this was due to concurrent reasons in three of them: One patient suffered a *Coxsackie-B* virus infection, one patient was concurrently treated with anti-thymocyte globulin, and one with erythromycin). The last patient had a 3 fold rise of both transaminases only attributable to the study drug, which returned to normal after teicoplanin was discontinued.

FIGURE 1



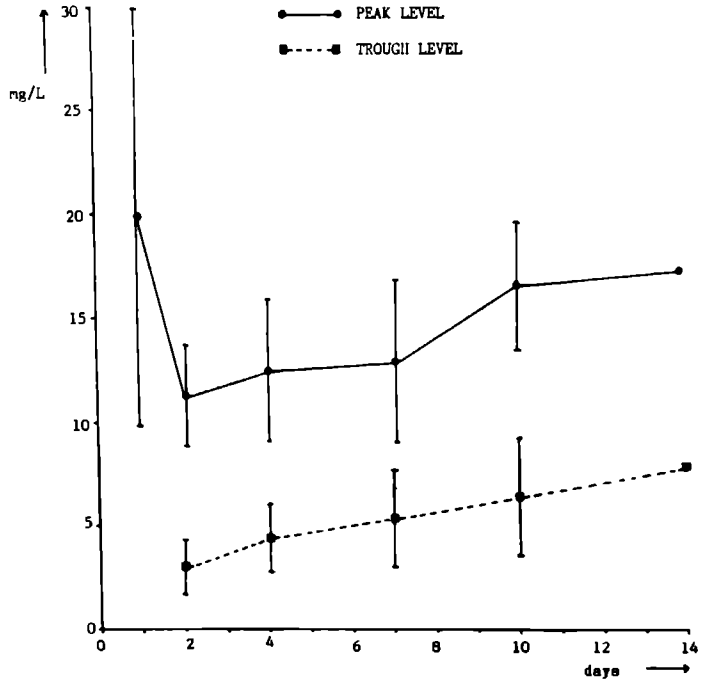
Scatterdiagram of changes in hearing sensitivity (ΔS) by pure tone audiogram before and after treatment with teicoplanin.

The concentration of teicoplanin in the sera determined by bioassay is shown graphically in figure 2. The mean peak level ± standard deviation (and range) was for day 1: 19.9 ± 10.1 (9.3-42.5) mg/L, day 2: 11.2 ± 2.3 (6.3-16.9) mg/L, day 4: 12.4 ± 3.4 (7.8-20.0) mg/L, day 7: 12.9 ± 3.9 (5.3-20.0) mg/l, day 10: 16.5 ± 3.1 (10.5-18.8) mg/L and day 14 only one sample: 17.1 mg/L. The through values were respectivly day 2: 3.0 ± 1.3 (2-6.3) mg/L, day 4: 4.4 ± 1.6 (2.2-6.7) mg/L, day 7: 5.3 ± 2.3 (2.2-8.8) mg/L, day 10: 6.3 ± 1.8 (3.8-8.2) mg/L and one sanple on day 14: 7.8 mg/L.

DISCUSSION

The data from this study shows that teicoplanin in combination with ceftazidime is an effective and safe drug for the treatment of Gram-

FIGURE 2



TEICOPLANIN SERUM LEVEL (N=20) BIOLOGICAL ASSAY

positive infections in the neutropenic patient. More than 90% of bacteriologically proven Gram-positive infections were cured by the combination. In six cases the causative pathogen was resistant to ceftazidime and all were eradicated. In the other 4 cases (2 *Staph. aureus* and 2 *Staph. epidermidis* all sensitive to ceftazidime) the causative pathogens were only eliminated after the addition of teicoplanin. Not all patients were neutropenic when teicoplanin was added to the empirically instituted ceftazidime monotherapy, which may have contributed to the good results obtained. However 64% of the patients were still neutropenic when responding to teicoplanin.

In contrast with the clinical study of Glupczynski et al (25) we saw no persistence or recurrence of the pathogens. This difference may be partly due to the possible synergistic effect of combined treatment of ceftazidime plus teicoplanin. At least the combination may have saved the patients from Gram-negative superinfections, which can be rapidly fatal in the neutropenic host.

Teicoplanin was well tolerated. We did not observe any alteration of the renal function, nor could ototoxicity be shown by single tone audiometry during treatment or follow-up. A three to seven fold rise of transaminases was found in 4 patients, but was considered to be due to concurrent hepatotoxic factors in three of them. In one patient a three fold transient rise of glutamic-oxaloacetic and glutamic-pyruvic transaminase was observed and was most likely due to the combination of teicoplanin with ceftazidime. After withdrawal of both drugs a rapid return to normal values was seen.

Based on the results of this study we conclude that teicoplanin in combination with ceftazidime is a safe and effective drug for Gram-positive infections in neutropenic patients.

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REFERENCES

1. De Pauw BE, Kauw F, Huytjens H, Williams KJ, and Bothof T. Randomized study of ceftazidime versus gentamycin plus cephotaxime for infections in severe granulocytopenic patients. J. Antimicrob. Chemother. (83) 12 Suppl. A; 93-99.
2. Donnelly JP, Marcus RE, Goldman JM, et al. Ceftazidime as first-line therapy for fever in acute leukemia. J. Infection (85) 11; 205-215.
3. Fainstein V, Bodey GP, Elting L, Bolivar R, Keating MJ, McCredie KB, and Valdivieso M. A randomized study of ceftazidime compared to ceftazidime and tobramycin for the treatment of infection in cancer patients. J. Antimicrob. Chemother. (83) 12 Suppl. A; 101-110.
4. Pizzo PA, Thaler M, Hathorn J, et al. New beta-lactam antibiotics in granulocytopenic patients, new options and new questions. Am. J. Med. (85) 79 Suppl. 2A; 75-82.
5. Bodey GP, Rodriguez V, Valdivieso M, and Feld R. Amikacin for treatment of infections in patients with malignant diseases. J. Inf. Dis. (76) 134; s421-s427.
6. Fainstein V, Bodey GP, Bolivar R, et al. Moxalactam plus ticarcillin or tobramycin for treatment of febrile episodes in neutropenic cancer patients. Arch Intern. Med. (84) 144; 1766-1770.
7. Keating MJ, Bodey GP, Valdivieso M, and Rodriguez V. A randomized comparative trial of three aminoglycosides comparison of continuous infusions of gentamicin, amikacin and sisonycin conbined with carbenicillin in the treatment of infections in neutropenic patients with malignancies. Medicine (79) 58; 159-170.
8. Winston DJ, Ho WG, Young LS, Hewitt WL, Gale RP. Piperacillin plus amikacin therapy v carbenicillin plus amikacin therapy in febrile, granulocytopenic patients. Arch. Int. Med. (82) 142; 1663-1667.
9. Rolinson GN. Beta-lactam antibiotics. J. Antimicrob. Chemoth. (86) 17; 5-36.
10. Bodey GP, Bolivar R, Fainstein V. Infectious complications in leukemic patients. Sem. Hematology (82) 19; 193-226.
11. Brown AE. Neutropenia, fever, and infection. Am. J. Med. (84) 76; 421-428.
12. Wade JC, Schimpff SC, Newman KA, and Wiernik PH. ***Staphylococcus epidermidis***: An increasing cause of infection in patients with granulocytopenia. Ann. Int. Med. (82) 97; 503-508.
13. De Pauw B, Williams K, de Neeff J, Bothof T, de Witte T, Holdrinet R, and Haanen C. A randomized prospective study of ceftazidime versus ceftazidime plus flucloxacillin in the empiric treatment of febrile episodes in severely neutropenic patients. Antinicrob. Ag. Chemother. (85) 28; 824-828.
14. De Pauw BE, Bothof T, Williams K, Holdrinet R, and de Witte T. A randomized study of ceftazidime versus ceftazidime plus cephalothin in febrile neutropenic patients. 14th ICC. Kyoto, (85) S. P52 abstr. 54.
15. Bardone MR, Paternoster M, and Coronelli C. Teichomycins, new antibiotics from *Actinoplanes teichomyceticus* nov. sp. II. Extraction and chemical characerization. J. Antibiot. (78) 31; 170-177.
16. Parenti F, Beretta G. Berti M, and Arioli V. Teichomycins, new antibiotics from *Actinoplanus teichomyceticus* nov. sp. I. Description of the producer strain, fermentation studies and biological properties. J. Antibiot. (78) 31; 276-283.

17. Somma S, Gastaldo L, and Corti A. Teicoplanin, a new antibiotic from *Actinoplanes teichomyceticus* nov. sp. Antimicrob. Ag. Chemother. (84) 26; 917-923.
18. Neu HC, and Labthavikul P. In vitro activity of teichomycin compared with those of other antibiotics. Antimicrob. Ag. Chemother. (83) 24; 425-428.
19. Verbist L, Tjandramaga B, Hendrickx B, et al. In vitro activity and human pharmacokinetics of teicoplanin. Antimicrob. Ag. Chemother. (84) 26; 881-886.
20. Traina GL, and Bonati M. Pharmacokinetics of teicoplanin in man after intravenous administration. J. Pharmacokin. Biopharmac. (84) 12; 119-128.
21. Williams AH, Gruneberg RN. Teicoplanin. J. Antimicob. Chemother. (84) 14; 441-448.
22. Moellering RC jr. Pharmacokinetics of vancomycin. J. Antimicrob. Chemother. (84) 14 Suppl. D; 43-52.
23. Sorrell TC, and Collignon PJ. A prospective study of adverse reactions associated with vancomycin therapy. J. Antimicrob. Chemother. (85) 16; 235-241.
24. Fainstein V, LeBlanc B, and Bodey GP. Comparative in vitro study of teichomycin A2. Antimicrob. Ag. Chemother. (83) 23; 497-499.
25. Glupzynski Y, Lagast H, van der Auwera P, et al. Clinical evaluation of teicoplanin for therapy of severe infections caused by Gram-positive bacteria. Antimicrob. Ag. Chemother. (86) 29; 52-57.
26. McElrath MJ, Goldberg D, Neu HC. Allergic cross-reactivity of teicoplanin and vancomycin. The Lancet (86) I; p47.
27. Bauer a, Kirby W, Sherris T. Antibiotic susceptibility testing by standardized single disc method. Amer. J. Clin. Pathol (66) 45; 493-496.
28. Barry AL, Thornsberry C, and Jones RN. Evaluation of teicoplanin and vancomycin disk susceptibility tests. J. Clin. Microbiol. (86) 23; 100-103.

CHAPTER 6

CEFTAZIDIME ALONE FOR TREATING PSEUDOMONAS AERUGINOSA SEPTICAEMIA IN NEUTROPENIC PATIENTS. *

C. VERHAGEN*, B.E. DEPAUW*, J.P. DONNELLY**, K.J. WILLIAMS+, T. DE WITTE* and J.TH.P. JANSSEN*.

* Division of Haematology, Department of Internal Medicine, University Hospital St Radboud, Nijmegen, The Netherlands
** Department of Bacteriology, Royal Postgraduate Medical School, Hammersmith Hospital, London, U K
\+ Glaxo Group Research, Greenford, Middlesex, U K

* **(Published "Journal of Infection" (1986) 13, 125-131).**

SUMMARY

Twenty nine patients with prinary or secondary hypoplastic bone marrow were treated successfully with ceftazidime alone for established septicaemia caused by *Pseudomonas aeruginosa* of which 38% strains were gentamicin-resistant. All the patients were neutropenic at the start of therapy; most were cured with microbiological confirmation before the bone marrow had regenerated. One patient died of cerebral haemorrhage due to profound thrombocytopenia without evidence of infection at autopsy. Significant toxicity was not observed. Ceftazidime alone is, therefore a safe and effective treatment for infections caused by this organism even in the neutropenic patient.

INTRODUCTION

Ceftazidime has a broad spectrum of activity which includes *Pseudomonas aeruginosa* (1,2) and has been shown to be an effective drug for infections caused by this organism (3-7). In these studies, patients had a wide variety of underlying diseases, but experience in treating the neutropenic patient, who represents perhaps the ultimate challenge for any antibiotic, is limited. Despite its decreasing incidence, *Ps. aeruginosa* infection remains a major threat to the neutropenic host (8). Mortality rates up to 57% within 24 hours in neutropenic patients not receiving appropriate therapy have been described. If prompt appropriate therapy is begun, cure rates of 41% to 80% with a mean of 65% may be achieved (9,10). Synergistic combinations of either an aminoglycoside plus a beta-lactam antibiotic or two beta-lactams have been used to offer the best chance of cure (11). Aminoglycosides, however, are associated with side effects particularly when given concurrently with agents that potentiate nephrotoxicity (12-14) and antagonism between beta-lactams may arise unpredictably. For these reasons, single drug therapy may be preferred. As a result of our studies of infection inneutropenic patients (15-17), we now have firm evidence that this drug provides effective treatment for septicaemia caused by *Ps. aeruginosa*.

PATIENTS AND METHODS

Between 1981 and May 1985, 352 neutropenic patients with febrile episodes have been treated with ceftazidime alone or with combinations of drugs as empirical treatment in several prospective randomised studies (15-17). Their records were reviewed in order to identify those with patients from whom *Ps. aeruginosa* had been isolated from at least one of three samples of venous blood taken at different times from three different sites. All patients were profoundly neutropenic at the onset of fever (see Table I), all were nursed in reversed-barrier isolation and all but three had received orally various forms of selective decontamination of the gut. This consisted of 960 mg co-trimoxazole 8 hourly, 100 mg polymyxine-B and 250 mg miconazol or 400 mg amphotericin-B 6 hourly. When broad-spectrum antibiotics had to be started, selective decontamination of the gut was discontinued, except of the antifungal compound, and was reinstituted as

TABLE I

Days of fever, symptoms, therapy and neutrophil count of patients with *Pseudomonas* septicaemia.

Patient No.	Days of fever	Days of symptoms	Days of therapy	Neutrophils at ($\times 10^9$/L) Onset	Resolution
1	4	5	13	0.20	0.20
2	5	4	11	0.20	0.10
3	3	3	7	1.00	2.40
4	6	1	9	0.10	<0.10
5	8	1	18	<0.10	<0.10
6	2	2	6	<0.10	0.10
7	6	2	8	0.50	0.30
8	8	11	18	0.20	0.20
9	15	17	26	0.50	0.50
10	3	5	9	1.00	0.70
11	3	3	10	0.60	0.50
12	2	2	7	0.40	<0.10
13	12	16	19	0.90	1.00
14	1	5	9	0.40	0.20
15	2	2	7	0.10	0.70
16	4	8	13	0.40	0.50
17	16	21	31	<0.10	<0.10
18	4	4	7	0.20	0.40
19	3	3	9	0.10	0.50
20	11	11	15	0.80	0.50
21	9	9	14	<0.10	0.10
22	4	3	8	0.30	0.70
23	4	6	10	0.20	<0.10
24	4	4	11	0.30	0.10
25	4	3	7	0.30	0.40
26	1	2	7	0.70	0.50
27	1	1	6	0.20	0.10
28	20	21	26	0.10	0.30
29	2	2	9	<0.10	0.50
Mean	5.76	6.10	12.07	0.33	0.40

soon as the broad-spectrum antibiotics were discontinued. Ceftazidime (2g 8 hourly in a 30 min infusion) was given empirically as soon as a patient had been febrile (temperature $\geq$ 38.5 °C) for 2-3 h. One patient received a dose of 1g 6 hourly in order to adjust for a pre-existing impaired renal function. Concurrent administration of flucloxacillin or cephalothin was not considered ground for exclusion since neither drug is active against *Ps. aeruginosa*. Granulocyte transfusions were not given and patients were treated with ceftazidime for 4 days after resolution of fever with a minimum of 7 days treatment. Clinical cure was defined as complete resolution of all signs and symptoms without evidence of infection at the end of therapy or during immediate follow-up. Eradication of the organism without recurrence during the subsequent 4 weeks was considered to be a satisfactory microbiological response. Full records included a complete history, physical examination, chest X-ray and the results of regular cultures obtained from the throat, faeces, urine, sputum and blood. Haematological (Hemalog D Technicon Instruments, Tarrytown, NY, U.S.A.) and biochemical profiles were obtained three times weekly. Strains of Ps. aeruginosa were characterised by growth on cetrimide agar at 42 °C, production of pyocyanin and detection of fluoroscein by illumination with ultra-violet light. Susceptibility to antibiotics was determined by means of the disc-diffusion method of Kirby-Bauer (18). For ceftazidime, zones of inhibition of more than 16 mm were classified as susceptible, zones of inhibition less than 14 mm as resistant and the remainder as intermediate.

RESULTS

Of 29 patients treated with ceftazidine, nine had received other antibiotics concurrently (cephalothin five patients, flucloxacillin four patients). Five patients were changed to ceftazidime having failed to respond to gentamicin plus a cephalosporin. All but four patients had malignant disease of the bone marrow. Of these, 14 were diagnosed as having acute myeloid leukaemia. Two of the patients were given allogeneic bone marrow transplants and both survived. Other details are shown in Table II. Nine patients had clinical evidence of tissue infections of which 7 were localised in the respiratory tract, five patients having bronchopneumonia.

TABLE II

Clinical data of the patients with *Pseudomonas* septicaemia.

Patient No.	Age (years)	Sex	Underlying disease	Clinical infection	Previous therapy	Additional therapy	Colonisation.
1	29	F	AML	S	SGD		
2	43	F	AML	S	SGD		
3	37	M	AML	S+Pharyngitis	SGD		
4	29	M	AML	S	SGD		
5	18	F	AML	S+Cellulitis	SGD		
6	40	M	AML	S	SGD		
7	16	M	AML	S+Shock	SGD		
8	35	M	AML	S+Bronchopn.	SGD		
9	34	F	AML	S+Bronchopn.	SGD		
10	22	M	AML	S	SGD		
11	48	M	AML	S			
12	16	M	AML	S	SGD		
13	49	M	AML	S+Bronchopn.	SGD	4x2g Cthn.	
14	58	M	AML	S	SGD+Gent. +Ctx.		
15	60	F	ALL	S	SGD+Gent. +Cfx.		*S.epid.*
16	63	F	ALL	S	SGD+Gent. +Cfx.		*S.faec.*
17	40	M	ALL	S+Cellulitis	SGD		
18	49	M	ALL	S	SGD	4x2g Fluc.	
19	38	M	ALL	S+Pharyngitis	SGD	4x2g Fluc.	
20	46	M	ALL	S	SGD	4x2g Fluc.	
21	39	M	LYMPHOMA	S+Bronchopn.	SGD	4x2g Fluc.	
22	71	F	LYMPHOMA	S	Gent.+Ctx.		
23	31	M	LYMPHOMA	S+Bronchopn.	Gent.+Cthn.		
24	56	M	APL.AN.	S+Shock	SGD		
25	64	M	APL.AN.	S	SGD	4x2g Cthn.	
26	37	M	APL.AN.	S	SGD	4x2g Cthn.	
27	15	F	HCL	S	SGD	4x2g Cthn.	
28	64	M	HCL	S	SGD	4x2g Cthn.	*C.alb.*
29	73	F	Solid T.	S	SGD		
Mean	42						

SGD, Selective Gut Decontamination; S, Septicaemia; AML, Acute Myeloid Leukaemia; Bronchopn, Bronchopneumonia; Cthn, Cephalothin; Gent, Gentamicin; Ctx, Cefotaxim; Cfx, Cefuroxim; ALL, Acute Lymphoblastic Leukaemia; *S.epid*, *Staphylococcus epidermidis*; *S.faec*, *Streptococcus faecalis*; Fluc, Flucloxacillin; APL.AN, Aplastic Anaemia; HCL, Hairy Cell Leukaemia; *C.alb*, *Candida albicans*; Solid T, Solid Tumor.

Shock was diagnosed in two patients both of whom presented with hypotension, rigors and peripheral vascular collapse. They were treated concomitantly with infusions of plasma. One patient died on the 6th day of treatment from cerebral haemorrhage which was attributed to profound thrombocytopenia. Blood cultures had become sterile on 3rd day. Evidence of infection was not found post mortem. Clinical cure and complete eradication of *Ps. aeruginosa* were observed in all 29 cases. Blood, sputum and mouthwashes became bacteriologically negative; neither colonization nor recurrence was observed during surveillance for at least 4 weeks. All patients were neutropenic at the onset of fever with a mean neutrophil count of 0.33×10^9/L. Five patients had an increase of their neutrophil count during therapy of more than 0.25×10^9/L, but in only one did the neutrophil count exceed 1.0×10^9/L during this period. Neutropenia following cessation of antibiotics continued for a mean of 4 days (range 0-14 days). Patients were febrile for a mean of 5.7 days (range 1-20), but their symptoms were present for longer (mean 6.6 days: range 1-21) and they received therapy for a mean duration of 12.1 days (range 6-31). In patients with a clinical focus fever took longer to subside than it did in those without (median 8 days vs. 4 days: $0.01<p<0.05$ Rank Sum test), their symptoms persisted longer (11 days vs. 3 days: $0.001<p<0.01$) and they received significantly more therapy (18 vs. 9 days: $0.001<p<0.01$). All strains of *Ps. aeruginosa* were susceptible to ceftazidime compared with 52% that were susceptible to gentamicin (Table III). Serious adverse effects were not seen during this study. One patient developed a transient moderate rise of the serun transaminases, tolerated with continuation of ceftazidime

TABLE III

In-vitro Susceptibilities of the strains of *Pseudomonas aeruginosa* isolated

Antibiotic	Susceptible N (%)	Intermediate N (%)	Resistant N (%)
Gentamicin	15 (52)	3 (10)	11 (38)
Tobramycin	23 (79)	2 (7)	4 (14)
Amikacin	23 (79)	4 (10)	2 (7)
Azlocillin	17 (58)	6 (21)	6 (21)
Carbenicillin	17 (59)	4 (14)	8 (28)
Piperacillin	18 (62)	3 (10)	8 (28)
Cefsulodin	21 (72)	-	8 (28)
Ceftazidime	29 (100)	-	-

and reversible after the drug was withdrawn. Three patients became colonized by other micro-organisms, one with *Candida albicans*, one with *Staphylococcus epidermidis* and one with *Streptococcus faecalis*. Drug related nephrotoxicity was not registered.

DISCUSSION

Before effective therapy was available 16% of cancer patients with septicaemia caused by *Ps. aeruginosa* died within the first 12 hours and 30% died within a day of the organism being isolated from the blood (19). The same figures are found today if inappropriate therapy is instituted (10). This study clearly demonstrates the potency of ceftazidime as anti-pseudomonal therapy even though most patients were severely neutropenic. The average time taken to effect cure was 6 days which is longer than many protocols allow before modifying therapy. Most patients with uncomplicated bacteraemia were free of symptoms within 4 days, whereas those in whom localised infection was diagnosed required longer treatment. Donnelly and colleagues (20) reported similar findings and suggested that in these circumstances additional antibiotics might be required to assist in better penetration or accelerated killing of bacteria. Since the ultimate outcome was excellent in both groups of patients a second antibiotic seems unnecessary unless faster resolution of symptoms can be shown. These results are better than those obtained from treating similar infections with aminoglycosides. Only in non-neutropenic patients did the success rate for gentamicin or tobramycin given alone reach 30%. Patients with severe neutropenia and a susceptible organism had only a 29% cure rate if treated with aminoglycosides alone. Cure rates for an anti-Pseudomonal penicillin with or without an aminoglycoside did not differ and reached 72% (10,21). Single drug therapy for pseudomonas infections is more effective with ceftazidime than with any other single antibiotic. Furthermore, this drug results in cure rates similar to those achieved with combinations of other antibiotics.

The choice of drug depends, not only on its proven efficacy but also on the antibiotic susceptibility of the pathogens prevalent in the particular population of patients. Extensive use of single drug therapy requires vigilance since success depends upon continued susceptibility to the particular drug. In our experience, emergence of resistance to

ceftazidime has not arisen after 4 years of use nor has there been a shift in susceptibility patterns of prevalent pathogens. The potential for toxicity also influences the choice of antibiotic and becomes of crucial importance if it is to be administered with nephrotoxic drugs such as cis-II-platinum or cyclosporin A, both often required to manage malignant diseases or bone marrow transplant recipients (22). Moreover, as shown in this study, neutropenic patients often require prolonged courses of antibiotic therapy and aminoglycoside-related toxicity is generally believed to increases with the length and number of courses (23). Further studies (24,25) in febrile neutropenic patients also suggest that ceftazidime therapy alone is an effective and non-toxic alternative to combination therapy in the empirical treatment of the immuno-compromised host if one is prepared to modify therapy should infection by a resistant Gram-positive organism arise. Given its safety (26) and efficacy, ceftazidime may be considered as the drug of choice for first-line therapy of fever during neutropenia in patients at risk of ototoxicity and nephrotoxicity (2,15-17,20,24,25) and should prove highly effective for most infections caused by Gram-negative bacilli without the need to modify therapy.

REFERENCES

1. Bauernfeind A: An evaluation of the activity of cephalosporins against *Pseudomonas aeruginosa*. J.Antimicrob.Chemother. 1981; 8, suppl. B: 111-115.
2. Standiford H, Drusano G, Fitzpatrick B, Tatum B, Schimpff S: Bactericidal activity of ceftazidime in serum compared with that of ticarcillin combined with amikacin. Antimicrob.Agents and Chemother. 1984; 26: 339-342.
3. Mastella G, Agostini M, Barlocco G et al: Alternative antibiotics for the treatment of pseudomonas infections in cystic fibrosis. J.Antimicrob.Chemother. 1983; 12, Suppl. A: 297-311.
4. Maslow M, Rosenberg A, Pollock A et al: Ceftazidime in infections caused by enterobacteriaceae and ***Pseudomonas aeruginosa***. J.Antimicrob.Chemother. 1983; 12, Suppl. A: 213-217.
5. Clumeck N, Gordts B, Dab I, Jaspar N, van Laethem Y, Butzler JP: Ceftazidime as a single agent in the treatment of severe ***Pseudomonas aeruginosa*** infections. J.Antimicrob.Chemother. 1983; 12, Suppl. A: 207-211.
6. van Dalen R, Muytjens H, Gimbrere J: Ceftazidime in intensive care patients. J.Antimicrob.Chemother. 1983; 12, Suppl. A: 189-197.
7. Eron L, Park C, Nixon H: Ceftazidime in patients with Pseudomonas infections. J.Antimicrob.Chemother. 1983; 12, Suppl. A: 161-169.

8. Brown AE: Neutropenia, fever and infection. Amer.J.Med. 1983; 76: 421-428.
9. Singer C, Kaplan M, Armstrong D: Bacteremia and fungemia complicating neoplastic disease. Amer.J.Med. 1977; 62: 731-742.
10. Bodey GP, Jadeja L, Elting L: Pseudomonas Bacteremia. Retrospective analysis of 410 episodes. Arch. Intern. Med. 1985; 145: 1621-1629.
11. Pizzo PA, Commers J, Cotton D et al: Approaching the controversies in antibacterial management of cancer patients. Amer.J.Med. 1984; 76: 436-449.
12. Haas A, Anderson L, Lad T: The influence of aminoglycosides on the nephrotoxicity of cis-diaminodichloroplatinum in cancer patients. J.Infect.Dis. 1983; 147: 363.
13. Whelton A. Clinical strategies for the reduction of aminoglycoside nephrotoxicity and ototoxicity. Chemioterapia 1984; 3: Suppl. 5, 52-59.
14. Giamarellou H, Daphnis E, Pettrikos G, Kanellakopolou K, Emanouel G. Prospective comparitive evaluation of gentamicin, tobramicin, netilmicin and amikacin in the production of nephrotoxicity in man. Chemioterapia 1984; 3: Suppl. 5, 80-87.
15. de Pauw BE, Kauw F, Huytjens H, Williams K, Bothof Th: Randomized study of ceftazidime versus gentamicin plus cefotaxime for infections in severe granulocytopenic patients. J.Antimicrob. Chemother. 1983; 12, Suppl. A: 93-99.
16. de Pauw BE, Williams K, de Neeff J et al.: A randomized study of ceftazidime versus ceftazidime plus flucloxacillin in the empiric treatment of febrile episodes in severely neutropenic patients. Antimicrob. Ag. Chemother. 1985; 28: 824-828.
17. de Pauw BE, Bothof J, Williams K, Holdrinet R, de Witte T: A randomized study of ceftazidime alone versus ceftazidime plus cephalothin in febrile neutropenic patients. 14th ICC Kyoto, Jan.,June. 1985 Session P 52 abstract 54.
18. Bauer A, Kirby W, Sherris T: Antibiotic susceptibility testing by standardized single disc method. Amer.J.Clin.Pathol. 1966; 45: 493-496.
19. Whitecar J, Bodey G, Luna M: Pseudomonas bacteremia in cancer patients. Amer.J.Med.Sci. 1970; 260: 216-223.
20. Donnelly JP. Marcus RE, Goldman JM et al: Ceftazidime as first line therapy for fever in acute leukaemia. In press J. of Inf. 985; 11: 205-215.
21. Bodey G: Aminoglycoside use in the compromized host. In: Whelton A, Neu H, Eds. The aminoglycosides. New York: Marcel Dekker Inc., 1982: 557-583.
22. Bennet WM, Pulliam JP: Cyclosporin nephrotoxicity. Ann.Intern.Med 1983; 99: 851-854.
23. Bodey GP: Antibiotics in patients with neutropenia. Arch. Intern. Med. 1984; 144: 1845-1851.
24. Pizzo PA, Thaler M, Hathorn J et al. New beta-lactan antibiotics in granulocytopenic patients , new options and new questions. Am. J. Med. 1985; 79: Suppl. 2A, 75-82.
25. Fainstein V, Bodey GP: Single-agent therapy for infections in neutropenic cancer patients. Am.J.Med. 1985; 79, Suppl. 2A: 83-88.
26. Meyers BR: Comparative toxicities of third-generation cephalosporins. Am.J.Med. 1985; 79, Suppl. 2A: 96-103.

CHAPTER 7

CEFTAZIDIME DOES NOT ENHANCE CYCLOSPORIN-A NEPHROTOXICITY IN FEBRILE BONE MARROW TRANSPLANTATION PATIENTS. *

C. VERHAGEN*, B.E. DE PAUW*, T. DE WITTE*, R.S.G. HOLDRINET*, J.TH.P. JANSSEN* and K.J. WILLIAMS**.

* Division of Haematology, Department of Internal Medicine, University Hospital St. Radboud, Nijmegen, The Netherlands
** Glaxo Group Research, Greenford, Middlesex, United Kingdom.

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SUMMARY

Ceftazidime was used as monotherapy for 30 febrile episodes in 28 patients, who underwent allogeneic bone marrow transplantation and who were treated concomitantly with the immunosuppressive agent cyclosporin-A. Ceftazidime did not enhance the well established nephrotoxicity of cyclosporin-A as measured by serum creatinine levels or creatinine clearance. Although an increasing number of Gram-positive infections in these patients warrants vigilance, ceftazidine as initial empirical monotherapy proved to be successful in 95% of all febrile post-transplantation patients. All Gram-negative, and 69% of the Gram-positive infections were cured with ceftazidime alone. The overall clinical cure rate was 72%, with microbiological clearance in 63%. This compares favourably with aminoglycoside containing schedules, and avoids the aminoglycoside associated nephrotoxicity.

INTRODUCTION

In the last decade, allogeneic bone marrow transplantation has been shown to provide a possibility for curative correction of a number of lethal conjenital and acquired disorders of the haematopoietic and lymphoid systems (16). Infections and graft-versus-host disease, however, remain major obstacles to the success of a bone marrow transplant. Several approaches have been proposed to prevent or treat acute graft-versus-host disease. The addition of cyclosporin-A has been a step forward and proved even to be associated with a faster engraftment (6). The major side-effect, however, is dose related nephrotoxicity (2,7,9,20), which is enhanced by important antimicrobial agents such as intravenous amphotericine B (10), aminoglycosides (22), and co-trimoxazole (19). In the present study we report on the combination of cyclosporin-A and ceftazidime, a third generation cephalosporin (12), with activity comparable to the aminoglycosides (5,13-15), in febrile bone marrow transplant patients.

PATIENTS AND METHODS

All patients, who underwent allogeneic bone marrow transplantation and who were treated with cyclosporin-A, from July 1983 until February 1985 were included in this study. Bone marrow donors were histocompatible siblings, except one patient, who received marrow from a haplo-identical brother (pt. 22). All but two were suffering from haematological malignancies (Table I). Transplant conditioning was done as previously described (24). All patients were nursed in single rooms with filtered air under positive pressure throughout the transplant period. All received oral selective gut decontamination (ciprofloxacin or pipemidic acid, and amphotericine B), herpes virus prophylaxis with acyclovir orally, and all fenales received lynoestrenol. Cyclosporin-A was given 3 mg/kg continuously intravenously from day -1 to +28 from transplantation, followed by 3x3 mg/kg/day orally with a gradual tapering off after eight weeks with 50-100 mg/week and discontinuation after twelve weeks. The dose was adjusted according to trough serum levels (400-600 ng/ml) and serum creatinine if necessary or after the occurrence of other side effects, such as hepatotoxicity, tremors, skin eruptions, hyperaesthesia or gum hypertrophy. Ceftazidime (2g 8 hourly in 30 min. iv. infusion) was given empirically as soon as a

patient had become febrile (temperature >38.5 °C) for more than three hours. Only one patient got a reduced dose (1g 8 hourly as a 30 min. infusion) in order to adjust for a pre-existing renal impairment. Pretreatment evaluation, culturing and follow up was done as previously described (13). Three blood cultures were taken, one hour appart from different sites with 20 cc blood to improve the chance of a positive culture. This was repeated as long as a patient remained febrile. Serum creatinine levels were followed daily and the urine was examined for casts and protein. Creatinine clearance was calculated from the serum creatinine and 24 hours urine creatinine excretion. Haematological (Hemalog D, Technicon Instruments Tarrytown, NY, USA) and biochemical profiles were obtained three times weekly.

All febrile patients, who received cyclosporin-A after bone marrow transplantation and who were treated concomitantly with ceftazidime for at least 48 hours were assessable to evaluate toxicity. All patients who were treated with ceftazidime for at least 48 hours, including those who changed because of therapy failure within that time, were assessable to study the efficacy of ceftazidime monotherapy as initial empiric treatment. Failure of initial empiric treatment was defined as mortality due to infection within 48 hours after therapy had started and infection related death afterwards if another initial therapy could possibly have prevented an eventually lethal outcome. Clinical or microbiological success of ceftazidime monotherapy was defined as cure without the need of modification. A clinical cure was defined as complete resolution of all signs and symptoms with no evidence of infection at the end of therapy or during immediate follow-up. Eradication of the organism with no recurrence during the subsequent four weeks was considered a satisfactory microbiological response. A superinfection was defined as any new acquired infection during treatment or within 48 hours after finishing ceftazidime monotherapy, which then required subsequent therapy.

RESULTS

All thirty-eight consecutive transplanted patients who received cyclosporin-A were eligible for this study. Seven patients never experienced any febrile periods. The renaining thirty-one had altogether 33 febrile episodes. Three patients were not assessable to evaluate toxicity as

they received ceftazidime for less than 48 hours. Two of these patients died due to a relapse of their leukemia within 2 days after becoming febrile. The third patient was reallocated to a combination of cephalothin and vancomycin within 24 hours, because the blood cultures showed growth of *Staphylococcus epidermidis* and *Streptococcus viridans*. Both microorganisms however were later shown to be susceptible to ceftazidime by disktesting. Thirty febrile episodes in 28 bone marrow recipients, were therefore eligible for toxicity analysis. The age of these patients ranged from 16 to 40 years with a mean of 27 years, thirteen were females and fifteen males. The diagnosis and demographic details are shown in Table I.

TABLE I

Clinical data of the transplanted patients with febrile episode(s).

Patient number	Age years	Sex	Underlying disease	Clinical infection	Isolated Microorganism(s).
1	24	F	AML	Sepsis	*Streptococcus viridans*
2	26	F	AML	Sepsis	*Streptococcus viridans*
3	32	M	AML	Sepsis	*Staphylococcus epidermidis*
4	27	F	AML	Pharyngitis	-
5	18	F	AUL	Sepsis	*Streptococcus viridans*
6	21	F	ALL	FUO	-
7	16	M	ALL	Sepsis	*Pseudomonas aeruginosa*
7*	..	.	...	Pharyngitis	-
8	24	F	ALL	FUO	-
9	17	F	ALL	Drug Fever	-
10	19	M	ALL	TBI	-
11	22	M	ALL	FUO	-
12	30	F	ALL	AGvHD	-
13	30	F	ALL	Sepsis	*Acinetobacter species*
14	34	F	CML	FUO	-
15	40	M	CML	Sepsis	*Streptococcus sanguis*
16	22	M	CML	Sepsis	*Staphylococcus epidermidis*
17	40	M	CML	FUO	-
17*	..	.	...	Sepsis	*Streptococcus viridans*
18	37	M	CML	Bronchopn.	*Klebsiella pneumoniae*
19	37	F	CML	Bronchopn.	*Bacteroides melanogenicus*
20	16	M	CML	Sepsis	*Pseudomonas aeruginosa*
21	36	M	CML	Sepsis	*Staphylococcus epidermidis*
22	21	F	CML	Sepsis	*Lactobacillus casei*
23	18	M	CML	FUO	-
24	39	M	CML	Sepsis	*Staphylococcus epidermidis*
25	32	M	CML	Bronchopn.+ sepsis	*Staphylococcus aureus*
26	30	F	Apl. An.	AGvHD	-
27	17	M	Apl. An.	Sepsis	*Staphylococcus epidermidis*
28	25	M	NHL	Sepsis	*Staphylococcus aureus* & *Staphylococcus epidermidis*
Mean	26.7				

* Second febrile period
AML= Acute Myeloid Leukemia, AUL= Acute Undifferentiated leukemia, ALL= Acute Lymphoblastic leukemia, CML= Chronic Myeloid Leukemia, Apl. An.= Aplastic Anaemia, NHL= Non Hodgkin Lymphoma, FUO= Fever of Unknown Origin, TBI= Total Body Iradiation, AGvHD= Acute Graft-Versus-Host Disease, Bronchopn.= Bronchopneumonia.

There was no need to adjust the cyclosporin-A dosage due to a rise in serum creatinine in any individual patient during ceftazidime treatment. The mean

± Standard Deviation of the levels of the serum creatinine before the start of ceftazidime was 81 ± 35 umol/L. (range 44-216). The mean ±SD of the highest values during treatment was 83 ± 37 umol/L. (range 45-234), and ten days after termination of ceftazidime 79 ± 35 umol/L. (range 44-222). The maximum rise of serum creatinine of 18 umol /L. was observed in patient 17* during a second febrile period when he developed acute graft-versus-host disease. After high dose corticosteroids a return to the normal level was noted without adjustment of the drug dosages. None of the patients showed occurrence of casts nor development of significant protein loss in the urin. The calculated creatinine clearance did neither change during therapy (Table II), nor was an enhancement by ceftazidime of other potential adverse effects of cyclosporin-A seen in any patient.

TABLE II

Serum creatinine (and clearance) before, after and maximum levels during therapy with ceftazidime and cyclosporin-A concomitantly.

PATIENT NUMBER	SERUM CREATININE umol/L. (clearance ml/min) Pretreatment	Peak levels	during Follow up.
1	54 (91)	49 (100)	51 (96)
2	72 (67)	80 (63)	90 (58)
3	56 (130)	55 (130)	46 (130)
4	47 (130)	53 (130)	47 (130)
5	53 (130)	52 (130)	69 (130)
6	62 (128)	59 (130)	70 (99)
7	63 (107)	69 (124)	67 (120)
7*	79 (85)	78 (93)	63 (97)
8	56 (90)	45 (109)	45 (109)
9	48 (130)	50 (129)	44 (130)
10	55 (130)	55 (122)	44 (130)
11	72 (130)	71 (130)	75 (130)
12	100 (78)	81 (90)	71 (110)
13	132 (46)	134 (57)	95 (71)
14	140 (49)	117 (56)	123 (39)
15	92 (118)	104 (101)	107 (88)
16	125 (95)	122 (103)	121 (104)
17	89 (94)	90 (78)	104 (88)
17*	216 (40)	234 (39)	222 (39)
18	90 (128)	92 (119)	91 (120)
19	104 (51)	120 (46)	- (-)
20	44 (130)	48 (130)	48 (130)
21	58 (109)	64 (98)	58 (109)
22	64 (130)	75 (121)	68 (130)
23	71 (124)	81 (120)	64 (130)
24	80 (116)	92 (105)	89 (102)
25	88 (130)	86 (128)	95 (105)
26	79 (130)	98 (119)	87 (129)
27	75 (130)	72 (130)	62 (130)
28	57 (130)	70 (130)	76 (101)
Mean:	81 (106)	83 (105)	79 (106)

* Second febrile period.

Another five patients were not assessable with respect to the efficacy of ceftazidime as initial empiric monotherapy. Two patients developed acute graft-versus-host disease with initial temperature rise. Ceftazidime was successfully replaced by systemic steroids. One patient had

a temporary temperature elevation on the second day of total body irradiation without signs of infection, or positive cultures. One patient had been treated concomitantly with vancomycin and was cured. The fith patient was initially treated with vancomycin for a temperature rise after bone marrow infusion without success. Ceftazidime was added, but the temperature turned out to be a drugfever. Twenty-five febrile episodes in 23 bone marrow recipients were assessable. Fourty-four percent of the patients had less than 250 granulocytes / mm^3 at the onset of fever. The same was found at the time they responded to treatment. Three patients had a significant rise of neutrophils during treatment. All other had stable or decreasing counts (Table III). Fifteen patients had septicaemia associated with chills, and five had localized tissue infections (three bronchopneumonia of which one associated with septicaenia and two pharyngitis). The remainder were suffering from fever of unknown origin. The majority of bacterial isolates were Gram-positive microorganisms (Table I).

TABLE III

Neutrophil count at onset and response of treated patients.

Granulocyte count	Nr. (%) of patients at onset	at response*
< 250/mm^3	13 (44%)	8 (44%)
250- 500/mm^3	7 (23%)	3 (17%)
501-1000/mm^3	3 (10%)	3 (17%)
>1000/mm^3	7 (23%)	4 (22%)

* Only successfully treated patients.

Ceftazidime monotherapy as initial empiric treatment was successful in 96% of all febrile episodes. None of the patients died within 48 hours due to infection. Two infection-related deaths occurred later. The first, patient 21, died with a persisting *Staph. epidermidis* infection, 61 days after acquiring the infection despite use of different drug combinations. The second, patient 19, died on the fourth day due to bronchopneumonia caused by Bacteroides melanogenicus although erythromycin had been added after 48 hours. Eighteen of the 25 courses (72%) resulted in a clinical cure, and 12 (63%) of the 19 microbiologically proven infections were cured with ceftazidime alone. Four patients who failed were rescued by vancomycin (nr. 1,16,25 and 27), and one by erythromycin (nr. 22) respectively. Failures were not correlated with neutrophil count, nor with tissue localisation, but due to infection with resistant microorganisms. The median duration of fever was 3 days, as was the median duration of symptoms. The median duration of therapy was 9 days. No colonisation occurred during ceftazidime therapy, but two patients developed a

superinfection. In one patient *Staph. epidermidis* was cultured 2 days after termination of ceftazidime therapy. He was treated successfully with vancomycin plus cephalothin. The other patient died due to an *Aspergillus fumigatus* infection despite parenteral amphotericine B.

Two patients (nr. 9 & 22) experienced drug fever and one of them developed an exanthematous rash (nr. 22). All symptoms subsided after discontinuation of ceftazidime.

DISCUSSION

Cyclosporin-A is widely used as a powerful immunosuppressive agent for organ transplantation (4,17) and has an important place in the prevention and treatment of acute graft-versus-host disease after bone marrow transplantation (8,18). Clinical use is hampered by its nephrotoxicity. Infections are almost inevitable in bone marrow transplantation procedures and even moreso when graft-versus-host disease has occurred (1,11,23). Schedules comprising aminoglycosides have an established use in the empiric treatment of febrile neutropenic patients (3). The combined use of cyclosporin-A and aminoglycosides, however, will be limited by their additional nephrotoxicity, but restriction of cyclosporin-A would endanger the patient for developing acute graft-versus-host disease and inpair his resistance.

From this study it is evident that ceftazidime is a safe drug with no additional nephrotoxicity when used in combination with cyclosporin-A. As is already noticed by Pizzo (16) the spectrum of infecting pathogens in the neutropenic host is changing to more Gram-positive infections. We found comparable results in our study group with 68% Gram-positive isolates. This may reflect at least partially the successful selective oral gut decontamination, but also partially the increased use of indwelling catheters (21). Ceftazidime, an effective drug against aerobic Gram-negative organisms, is less active in Gram-positive infections. Nevertheless ceftazidime proved to be a safe drug for initial empiric monotherapy in this study. No patient died during initial treatment due to infection, and only one infection-related late death would have possibly survived if the initial therapy had included drugs with a spectrum including anaerobic microorganisms. None of the established combination schedules, including those containing aminoglycosides, would have prevented

this fatality. For 90% of the patients it would not have been beneficial to be treated with such a combination. Clinical cure was obtained in 72% of the cases, and an additional 20% after modification of therapy. All Gram-negative isolates and even 69% of the Gram-positive isolates were susceptible to and eradicated by ceftazidime alone. With monotherapy, vigilance and continuous monitoring of the patient is warranted considering the possible occurrence or emergence of resistant microorganisms. In our experience, emergent resistance to ceftazidime in this particular patient population has not occurred after four years of continued use, nor has there been a change in susceptibility patterns of prevalent pathogens. Results of ceftazidime as empiric monotherapy in febrile neutropenic patients compare favourably to two and three drug containing regimens (3,5,13-15). Initial empiric therapy with ceftazidime in febrile neutropenic patients is advocated when there is no strong suspicion of Gram-positive infections. Time will be available to await the results of the cultures, saving the patient from the toxicity of combined drug regimens, especially when antibiotics are to be used concomitantly with cyclosporin-A.

REFERENCES

1. Atkinson K, Storb R, Prentice RL, Weiden PL, Witherspoon RP, Sullivan K, Noel D, Thomas ED (1971) Analysis of late infections in 89 long-term survivors of bone marrow transplantation. Blood 53: 720-731.
2. Bennet WM, Pulliam JP (1983) Cyclosporin nephrotoxicity. Ann. Intern.Med. 99: 851-854.
3. Bodey GP (1984) Antibiotics in patients with neutropenia. Arch. Intern.Med. 144: 1845-1851.
4. Cohen DJ, Loertscher R, Rubin MF, Tilney NL, Carpenter CB, Strom TB (1984) Cyclosporine: A new immunosuppressive agent for organ transplantation. Ann.Intern.Med. 101: 667-682.
5. Donnelly JP, Marcus RE, Goldman JM, Cohen J, Worsley AM, Catovsky D, Darrell JH, Want SV, Galton DAG (1985) Ceftazidime as first line therapy for fever in acute leukaemia. J. of Inf. 11: 205-215. 6.Hows JM, Kaffaf S, Palmer S, Harris R, Fairhead S, Gordon-Smith EC (1982) Regeneration of peripheral blood cells following allogeneic bone marrow transplantation for severe aplastic anaemia Brit.J.Haematol. 52: 551-558.
7. Hows JM, Chipping PG, Fairhead S, Smith J, Baughan A, Gordon-Smith EC (1983) Nephrotoxicity in bone marrow transplant recipients treaed with cyclosporin A. Brit.J.Haematol. 54: 69-78.
8. Kahan BD (1983) Meeting report: The first international congress on cyclosporin: Houston, Texas: May 16-19; Dial. Transplant. 12: 6320-6339.

9. Kahan BD, Dennett WH (1985) Cyclosporin-associated renal injury. Transplantation proceedings XVIII 4: Suplement I.
10. Kennedy MS, Deeg HJ, Siegel H, Crowley JJ, Storb R, Thomas ED (1983) Acute renal toxicity with combined use of amphotericine B and cyclosporin after marrow transplantation. Transplantation 35: 211-215.
11. Lum LG, Seigneuret MC, Storb R, Witherspoon RP, Thomas ED (1981) In vitro regulation of immunoglobulin synthesis after marrow transplantation I. T cell and B cell deficiencies in patients with and without chronic graft-versus-host disease. Blood 58: 431-439. 12. Neu HC (1982) The new beta-lactamase-stable cephalosporins. Ann. Intern. Med. 97: 408-419.
13. De Pauw BE, Kauw F, Muytjens H, Williams K, Bothof Th (1983) Randomized study of ceftazidime versus gentamicin plus cefotaxime for infections in severe granulocytopenic patients. J.Antimicrob. Ag.Chemother. 12, Suppl. A: 93-99.
14. de Pauw B, Williams K, de Neeff T, Bothof T, de Witte T, Holdrinet R, and Haanen C. (1985) A randomized prospective study of ceftazidime versus ceftazidime plus flucloxacillin in the empiric treatment of febrile episodes in severely neutropenic patients. Antimicrob. Ag. Chemother. 28: 824-828.
15. de Pauw BE, Bothof J, Williams K, Holdrinet R, de Witte T (1985) A randomized study of ceftazidime alone versus ceftazidime plus cephalothin in febrile neutropenic patients. 14th ICC Kyoto, June. Session P 52 abstract 54.
16. Pizzo PA, Ladisch S, Sinon RH, Gill F, Levine AS (1978) Increasing incidence of Gram-positive sepsis in cancer patients. Med.Pediatr Oncol. 5: 241-244.
17. Powles RL, Clinc MK, Spence D, Morgenstern G, Watson JG, Selby PJ, Woods H, Barrett A, Jameson B, Sloane J, Lawler SD, Kay HEM, Lauson D, McElwain TJ, Alexander P (1980) Cyclosporin A to prevent graft-versus-host disease in man after allogeneic bone marrow transplantation. Lancet I: 327-329.
18. O'Reilly RJ (1983) Allogeneic bone marrow transplantation: current status and future directions. Blood 62: 941-964.
19. Ringden O, Myrenfors P, Klintmalm G, Tyden G, Ost L (1984) Nephrotoxicity by co-trimoxazole and cyclosporin in transplanted patients. Lancet I: 1016-1017.
20. Shulman H, Striker J, Deeg HJ, Kennedy MS, Storb R, Thomas ED (1981) Nephrotoxicity of cyclosporin-A after allogeneic marrow transplantation. N.Engl.J.Med. 305: 1392-1395.
21. Wade JC, Schimpff SC, Newman KA, Wiernik PH (1982) Staphylococcus epidermidis: an increasing cause of infection in patients with granulocytopenia. Ann.Intern.Med. 97: 503-508.
22. Whiting PH, Simpson IG, Thomson AW (1983) Nephrotoxicity of cyclosporin in combination with aminoglycoside and cephalosporin antibiotics. Transplant.Proc. 15: 2702-2706.
23. Witherspoon RP, Storb R, Ochs HD, Flournoy N, Kopecky KJ, Sullivan KM, Deeg HJ, Sosa R, Noel DR, Atkinson K, Thomas ED (1981) Recovery of antibody production in human allogeneic marrow graft recipients: influence of time post-transplantation, the presence or absence of chronic graft-versus-host disease, and antithymocyte globulin treatment. Blood 58: 360-368.
24. De Witte T, Raymakers R, Plas A, Koekman E, Wessels H, Haanen C (1984) Bone marrow repopulation capacity after allogeneic bone marrow transplantation of lymphocytes depleted bone marrow using counterflow centrifugation. Transplantation 37: 151-155.

CHAPTER 8

DRUG INDUCED SKIN REACTIONS IN PATIENTS WITH ACUTE NON-LYMPHOCYTIC LEUKAEMIA. *

C. VERHAGEN, L.J.A. STALPERS, B.E. DE PAUW and C HAANEN.

Division of Haematology, Department of Internal Medicine, University Hospital St Radboud, Nijmegen, The Netherlan

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SUMMARY

The incidence of drug induced skin rashes and related factors were analysed in a retrospective study of 151 patients with acute non-lymphocytic leukaemia (ANLL). Ninety-one (60%) developed a drug related toxicodermia to one or more drugs during remission induction and maintenance therapy. The incidence of rashes was mainly confined to the blastic stage of leukaemia and occurred significantly less often during remission. Patients with acute myeloid leukaemia, FAB classification M1, M2 and M3 (M1-3) developed skin reactions more often than those of types M4 and M5 (M4-5). Women suffered more frequently from drug induced skin lesions than men. The incidence of drug associated rashes was significantly higher in patients with ANLL than in the general population for: Allopurinol (16%), co-trimoxazole (14%), miconazole (23%), and ketoconazole (13%). The incidence for the penicillins (12%) and cephalosporins (5%) was conform the upper limit as reported for the general population. Additional toxic effects of combined therapy could not explain the differences observed and a dearrangement of the immunesystem during the blastic stage of leukaemia is suggested.

INTRODUCTION

An increase in drug related skin rashes has been reported associated with viral infections. Well known is the ampicillin related toxicodermia in patients with mononucleosis infectiosa (1,2), and co-trimoxazole related skin rashes in patients with the acquired immunodeficiency syndrome (AIDS) (3). In other diseases with dearrangement of the immunesystem like chronic lymphatic leukaemia an increase in penicillin allergy has been reported (4), and an increase of piperacillin related rashes were found in patients with acute myeloid leukaemia (5).

By virtue of more intensive and aggressive chemotherapy it has become possible to induce remission in the majority of patients with acute leukaemia. Different measurements have been introduced to cope with complications due to the considerable suppression of the immunesystem after chemotherapy. Nursing in reversed isolation and antibiotics were introduced for total decontamination or selective gut decontamination in order to reduce the risk of infection. More drugs are used to support the patient, like allopurinol as uricosuricum, antiemetics, tranquillizers, oral estrogens to prevent menstrual bleeding in women, etc. Patients challenged with many drugs have an increased risk of developing toxic or allergic skin rashes (6). We performed a retrospective study to analyse the factors influencing the frequency of skin rashes and the chance of occurrence related to the different drugs in 151 acute non-lymphocytic leukaemia patients (ANLL). More then fifty percent developed a drug related skin rash during remission induction. It appeared that the risk of developing an exanthematic reaction is increased during remission induction.

PATIENTS AND METHODS

All newly diagnosed patients with ANLL admitted from Januari 1975 till Januari 1986 were eligible for this retrospective analysis. Excluded were all patients who underwent bone marrow transplantation, as their immunologic reactions may be influenced by the donor graft (7). All those patients who never completed a remission induction course or died within 10 days after diagnosis, were excluded also. Leukaemia was classified according to the "French-American-British" (FAB) classification.

Remission-induction courses were given according to EORTC protocols and evolved from monotherapy (1975) to polychemotherapy with cytosine arabinoside, adrianycin or daunorubicin and vincristine since 1977. Allopurinol as uricosuricum was given in daily doses of 300 mg during remission induction and consolidation courses. Before 1979 occasionally miconazole or co-trimoxazole were used as gut decontamination. Thereafter selective gut decontamination was performed on a regular base. Polymyxin-B (4x 100 mg daily) plus co-trimoxazole (4x 720 mg daily) and miconazole (3x 500 mg daily) or ketoconazole (200 mg once daily) were used orally. In case of adverse reactions, co-trimoxazole was replaced by pipimidic acid (4x 200 mg daily) and the imidazole antifungals by amphothericine-B (4x 400 mg) orally. Other supportive medication consisted of lynestrenol (5 mg daily) in all women of child bearing age, antiemetics (promethazine-chloorpromazine or metoclopromide-chloride), and broad spectrum antibiotics in case of infection (before 1981 a broad-spectrum penicillin with an aminoglycoside or cephalosporine; thereafter ceftazidime monotherapy. On indication additionally cephalothin, flucloxacillin or vancomycin were added).

Drug related toxicodermia was defined as all skin rashes, urticaria, angioneurotic oedema or fixed eruptions associated with any drug used. The majority of patients received multiple therapy. Drugs were withdrawn stepswise in case a skin reaction did occur. A relation with a certain drug was accepted if all signs and symptoms disappeared after withdrawal of that particular drug, and/or reappeared after rechallenging with the same drug. The incidence of rashes for each individual drug was expressed by the percentage of patients exposed to the drug who developed a toxicodermia. If more than one drug could be made responsible and no rechallenge was performed, then that case was only recorded and not included in the final calculations of rash incidence for the individual drugs.

Incidence of toxicodermia was related to the incidence as reported in the literature for non-selected patients (3-16). The influence of age, sex, underlying disease, leukopenia, stage of leukaemia, and concomitant use of allopurinol was analysed. Statistical mathematics were performed with the Chi-square test with Yates correction and the Rank-sum test.

Over the period Januari 1975 to Januari 1986, 193 newly diagnosed patients with ANLL were admitted. Fifteen patients underwent bone marrow transplantation and were excluded from the study. Twenty-one patients were not assessable as they died within 10 days after admission or before completion of a remission induction course, and 6 patients were lost to follow up. One-hundred and fifty-one patients were evaluable. Ninety-one (60%) developed a drug related toxicodermia during remission induction and maintenance therapy. Sixty-four (42%) against a single drug, 21 (14%) against two different drugs, 5 (3%) against three and 1 patient (1%) against four different drugs. The toxicodermia manifested itself mainly as a maculopapular, fine rash and was itching in about half the cases. Often the rash became secondary haemorrhagic as many patients were thrombocytopenic at the time of appearance. Less often the skin reaction manifested itself as urticaria, which mainly was associated with the penicillins. Angioneurotic edema presented itself only twice, both times associated with co-trimoxazole.

Table I

Drug induced skin reactions in ANLL.

Incidence drug rashes	Nr. reactions/ total patients challenged (%).	
During blastic stage of leukaemia	89/151 (59%)	
During leukaemia in remission	12/ 78 (15%)	($p < 0.0001$)*
Women	52/75 (69%)	
Men	39/76 (51%)	($p < 0.05$)

* Chi-square with Yates correction.

The incidence of drug eruptions was higher in women; 52 out of 75 (69%), than in men; 39 out of 76 (51%) ($p < 0.05$). Rashes also occurred more often in patients with FAB classification M1, M2, and M3 (M1-3); 55 out of 78 (71%), than patients with M4 and M5 (M4-5); 36 out of 73 (49%) ($p < 0.01$). The proportion of women was higher in the group M1-3 than M4-5, but even after correction significantly more patients with M1-3 got a drug associated rash. Eighty-nine out of 151 patients (59%) developed a toxicodermia during first remisson induction or during a relapse of the

leukaemia. Only 12 out of 73 patients (15%) undergoing maintenance therapy developed a skin rash. This difference was highly significant ($p < 0.0001$). See table I and II.

Table II

Drug induced skin reactions in AML and ALL.

Parameter	Nr. of reactions/ patients challenged (%)		
	M1-3	M4-5	(Chi-square)
Number of patients	78	73	
Men/Women	35/43	41/32	(NS)
Mean age ± SD (range) years	43.4 ± 16.4 (13-74)	44.9 ± 16.0 (15-73)	
Incidence of drug rashes:			
During total follow-up	55/78 (71%)	36/73 (49%)	($p < 0.01$)
During blastic stage*	54/78 (69%)	35/73 (48%)	($p < 0.05$)
During remission*	6/41 (15%)	6/37 (16%)	(NS)
* Incidence during blastic stage/ incidence during remission	$p < 0.0001$	$p < 0.001$	

Drugs frequently related with toxicodermia in this study were allopurinol, co-trimoxazole, miconazole, ketoconazole, and penicillins, less often involved were the cephalosporins. Together these drugs accounted for 89% (111 out of 125) of all drug-associated eruptions. Patients in the blastic stage of leukaemia were exposed to a mean of 4.0 of these drugs during remision induction. Less often patients in remission were exposed, a mean of 2.8 drugs during maintenance therapy. The overall incidence of drug eruptions in the blastic stage of leukaemia was 112 during 673 exposures (17%) and 13 during 220 exposures (6%) in patients in remission ($p < 0.0001$). Some of these drugs have been studied in more detail, see Table III.

Allopurinol has been used in 148 patients. Twenty-three (16%) developed a skin rash. Eighteen out of 77 (23%) patients with M1-3 and only 5 out of 71 (7%) patients with M4-5 ($p < 0.05$). Fifty-three patients used allopurinol during maintenance therapy. None of these patients in remission developed a toxicodermia. None of the AMLL patients treated with allopurinol had a notable renal impairment.

One-hundred and forty-eight patients received co-trimoxazole. Twenty (14%) developed a skin rash. The incidence was higher in patients with M1-3

Table III

Incidence of toxicodermia of some of the most frequent involved drugs.

Drug	Occurring during	Incidence (%) General population	Incidence/patients challenged (%) ANLL total	M1-3	M4-5	M1-3/M4-5 (Chi-square)
Allopurinol	Total follow-up	104/2394 (4.3%)	23/148 (16%)	18/77 (23%)	5/71 (7%)	($p < 0.05$)
	Remission-induction	(Reference 9)	18/148 (12%)	15/77 (19%)	3/71 (4%)	($p < 0.05$)
	Remission		0/ 53 -	0/25 -	0/28 -	-
	Relapsed leukaemia		10/ 55 (18%)	7/27 (26%)	3/28 (11%)	NS
Incidence:	in-general/ in ANLL		$p < 0.0001$	$p < 0.0001$	NS	
	blastic stage/ remission		$p < 0.005$	$p < 0.01$	NS	
Co-trimoxazole	Total follow-up	23/657 (3.5%)	20/148 (14%)	12/76 (16%)	8/72 (11%)	NS
	Remission-induction	(Reference 11)	15/145 (10%)	10/76 (13%)	5/69 (7%)	NS
	Remission		1/ 54 (2%)	1/29 (3%)	0/25 -	-
	Relapsed leukaemia		5/ 49 (10%)	2/23 (9%)	3/26 (12%)	NS
Incidence:	in-general/ in ANLL		$p < 0.0001$	$p < 0.0001$	$p < 0.01$	
	blastic stage/ remission		$p < 0.05$	NS	NS	
Miconazole	Total follow-up	23/418 (5.5%)	33/118 (28%)	20/56 (36%)	13/62 (21%)	NS
	Remission-induction	(Reference 13)	32/113 (28%)	19/53 (36%)	13/60 (22%)	NS
	Remission		1/ 35 (3%)	1/11 (9%)	0/24 -	-
	Relapsed leukaemia		5/ 35 (14%)	3/14 (21%)	2/21 (10%)	NS
Incidence:	in-general/ in ANLL		$p < 0.0001$	$p < 0.0001$	$p < 0.0001$	
	blastic stage/ remission		$p < 0.005$	NS	$p < 0.01$	
Ketoconazole	Total follow-up	10/1361 (0.7%)	10/ 57 (18%)	9/37 (24%)	1/20 (5%)	NS
	Remission-induction	(Reference 14)	4/ 48 (8%)	3/29 (10%)	1/19 (5%)	NS
	Remission		1/ 26 (4%)	1/17 (6%)	0/ 9 -	-
	Relapsed leukaemia		5/ 21 (24%)	5/14 (36%)	0/ 7 -	-
Incidence:	in-general/ in ANLL		$p < 0.0001$	$p < 0.0001$	NS	
	blastic stage/ remission		NS	NS	NS	

twelve out of 76 (16%), compared to M4-5: eight out of 72 (11%). During remission the incidence was much lower: one out of 51 ANLL (2%) ($p < 0.05$).

Miconazole was used prophylactically in 118 patients. Thirty three (28%) developed a rash; M1-3: 20 out of 56 (36%), M4-5: 13 out of 62 (21%). In contrast only one patient out of 35 (3%) in remission experienced a skin rash. This patient with M2 received miconazole intravenously for a suspected systemic mycosis. The difference was higly significant ($p < 0.005$).

Ketoconazole as an alternative for miconazole was prophylactically used in 57 patients. Ten (18%) developed a skin rash. Only 1 patient out of 20 (5%) with M4-5 and 9 out of 37 (24%) with M1-3. During remission 26 patients received ketoconazole and one developed a toxicodermia (4%). None of these differences were significant.

Eighty-nine of the patients received a penicillin derivate. Eleven patients (12%) developed a rash. Five during amoxycillin or ampicillin, 2 during flucloxacillin, 2 during carbenicillin and 2 during feneticillin therapy. None of the rashes was observed during remission. Patients with M1-3 showed more often a toxicodernia; Seven out of 46 (15%) compared with 4 out of 43 (9%) in M4-5.

Four out of 118 (3%) patients treated with a cephalosporin showed a drug related rash. Three during cephalothin, and one during ceftazidine. The latter patient had also shown an allergic skin rash to ampicillin on an earlier occasion. Incidence of skin rash due to cephalosporins was significantly less than due to penicillins ($p < 0.001$).

The mean duration of treatment before occurrence of a drug eruption was 3.1 ± 6.3 days for allopurinol, 11.3 ± 6.4 days for co-trimoxazole, 10.9 ± 6.6 days for miconazole and 9.9 ± 10.7 for ketoconazole. This was much shorter for the betalactam antibiotics; toxicodermia appeared after a mean of 4.7 ± 4.1 days for penicillins and 4.3 ± 2.7 days for cephalosporins ($p < 0.001$, Rank-sum test).

Incidental drug related toxicodermia was reported for cytarabin (3x), iodine (2x), amphotericine-B (1x), amikacin (1x), chloorhexidine (1x), cimetidine (1x), 5-flucytosin (1x), paracetamol (1x), ranitidin (1x), rifampicin (1x), and teicoplanin (1x).

A small group of patients were rechallenged with the same drug after developing toxicodermia. Twenty-seven out of 29 patients (93%) showed a drug eruption after re-exposure during remission induction for a relapse of their leukaemia. Only 2 out of 20 patients in remission (10%) developed a toxicodermia after re-exposure to the same drug ($p < 0.0001$). Seven other patients with a drug allergy who had not shown any drug eruption after re-exposure during maintenance therapy, got a full blown toxicodermia again after relapse of their leukaemia.

The incidence of drug induced skin eruptions was not related to age or degree of neutropenia.

DISCUSSION

Incidence of toxicodermia in the general population is 1-3% (17). In this analysis it became clear, that drug related skin rashes more often occurred in patients with AMLL. This was mainly due to the high incidence in patients with M1-3. Moreover this difference was established to be restricted to the blastic stage of the leukaemia. This may explain the clinical observation of changing sensitivity to drug induced rashes in individual patients. Striking is the identical clinical observation for patients with certain viral infections, like mononucleosis infectiosa, who also may show an increased drug sensitivity only during the active phase of

the infection. The immunological basis for this phenomenon is lacking (17).

The same relation was found for some of the known allergenic drugs that has been analysed separately. The incidence of allopurinol related skin rashes in the general population is 2-5% (3,9), the incidence for M1-3 during remission induction was 23% in this study ($p < 0.0001$), but normal during remission. Although an increase in allopurinol related skin rashes in patients with renal failure has been reported (10), this could not explain the difference observed as none of the ANLL patients had a notable renal impairement.

The incidence for co-trimoxazol related skin rashes at random is 1-4% (11). This is significantly less than the 16% occurrence in M1-3 ($p < 0.0001$) and 11% in M4-5 ($p < 0.01$). Only in patients with AIDS an increased incidence has been reported (3).

Skin rashes up to 25% have been reported after exposure to miconazole intravenously (12). In orally treated patients the incidence of toxicodermia is rare. Heel et al (13) report an incidence overall of 3-6%. This was significantly less than the incidence in both M1-3 (36%) ($p < 0.0001$) and M4-5 (21%) ($p < 0.0001$)

Incidence of ketoconazole induced rashes in the general population is less than 1% (14) In patients with ANLL toxicodermia occurred in 18% of the patients exposed to this drug ($p < 0.0001$).

In this study the penicillins and the cephalosporins showed predominantly an urticarial rash, which mainly has been associated with Type I allergic reactions and IgE antibodies. The use of these compounds was associated with an allergy incidence comparable to the higher limit found in the general population (15). And, also in contrast with the previously analysed drugs, a significantly shorter incubation period was found before a rash occurred. An increase of ampicillin related skin rashes was shown in patients treated concurrently with allopurinol (16). None of the patients in this study was treated simultaneously with allopurinol and ampicillin.

Toxic influence of concurrently used allopurinol does not explain this phenomenon, as only one quarter of the rashes occurred during allopurinol treatment. Besides, allopurinol was also employed in patients in remission and no increased rash incidence was found during maintenance therapy. Analysis of the toxic influence of combined treatment during the blastic stage of leukaemia showed that the risk of drug induced rashes was 33% in case two drugs were used concurrently, and 48% in case of triple treatment with known allergenic drugs. This difference explains itself by

unrelated addition of chances. Multiplication of toxicity in combined treatment during blastic stage of leukaemia cannot be the sole explanation of the difference found between the rash incidence during remission induction or during maintenance therapy of leukaemia.

An increased sensitivity (18) or imbalance of the immunesystem during the active phase of leukaemia could possibly acount for the differences observed (19, 20). Disruption of this ballance by the cytostatic therapy as Katz found in a mouse model (19) cannot be the sole explanation of this phenomenon. We could not prove a relation between leukopenia and toxicodermia incidence. Moreover, significantly less exanthema occurred during remission, although the same drugs were used for consolidation as were used during remission-induction.

To explain the discordance between M1-3 and M4-5, one has to accept a difference in dearrangement of the cellular immunesystem between these two forms of ANLL. It is tempting to speculate about a modulating role of the monocytoid cells in the acute myelomonocytic or monoblastic leukaemic subsets. The same acounts for the distinction between sexes.

The results of this retrospective analysis have made clear that there is an increased risk of drug induced toxicodermia in ANLL. This increased risk is mainly confined to the blastic stage of leukemia and more increased in women and patients with M1-3.

REFERENCES

1. Pullen H, Wright H, McC Murdoch J. Hypersensitivity reactions to antibacterial drugs in infectious mononucleosis. Lancet 1967; II: 1176-1178.
2. Lund EHA, Bergan T. Temporary skin reactions to penicillins during the acute stage of infectious mononucleosis. Scand. J. Inf. Dis. 1975; 7: 21-26.
3. Gordin FM, Simon GL, Wofsy CB, Mills J. Adverse reactions to trimethoprim-sulfamethoxazole in patients with the acquired immunodeficiency syndrome. Ann. Int. Med. 1984; 100: 495-499.
4. Cameron SJ, Richmond J. Ampicillin hypersensitivity in lymphatic leukemia. Scot. Med. J. 1971; 16: 425-427.
5. Mead GM, Smith AG. Allergic skin reactions to piperacillin in patients with acute leukaemia. Lancet 1985; II: 499.
6. Parker CW. Drug therapy Drug allergy (third of three parts) . Eng. J. Med. 1975; 292: 957-960.
7. Tucker J, Barnetson RStC, Eden OB. Atopy after bone marrow transplantation. Brit. Med. J. 1985; 290: 116-117.
8. Muggia FM, Ball ThJ, Ultmann JE. Allopurinol in the treatment of neoplastic disease complicated by hyperuricemia. Arch. Int. Med. 1967; 120: 12-18.
9. Rundles RW. Metabolic effects of allopurinol and allo-xanthine. Ann. Rheum. dis. 1965; 25: 615-620.
10. Wilson JD, Simmonds HA, Worth JDC. Allopurinol in the treatment of uremic patients with gout. Ann. Rheum. Dis. 1967; 26: 136-142.
11. Lawson DH, Jick H. Adverse reactions to co-trimoxazole in hospitalized medical patients. Am. J. Med. Sci. 1978; 275: 53-57.
12. Wade TR, Jones HE, Chanda JJ. Intravenous miconazole therapy of mycotic infections. Arch. Int. Med. 1979; 139: 784-786.
13. Heel RC, Brogden RN, Pakes GE, Speight TM, Avery GS. Miconazole: A preliminary review of its therapeutic efficacy in systemic fungal infections. Drugs 1980; 19: 7-30.
14. Heel RC, Brogden RN, Carmine A, Morley PA, Speight TM, Avery GS. Ketoconazole: A review of its therapeutic efficacy in superficial and systemic fungal infections. Drugs 1982; 23: 1-36.
15. Wright AJ, Wilkowske CJ. The penicillins Mayo Clin. Proc. 1983; 58: 21-32.
16. B.C.D.S.P. Boston University Medical Center. Excess of ampicillin rashes associated with allopurinol or hyperuricemia. N. Eng. J. Med. 1972; 286: 505-507.
17. VanArsdel PP. Drug allergy, an update. Med. Clin. N. Am. 1981; 65: 1089-1103.
18. Dunagin WG, Millikan LE. Drug eruptions. Med. Clin. N. Am. 1980; 64: 983-1003.
19. Katz DH. The allergic phenotype: Manifestation of "allergic breakthrough" and inbalance in normal "damping" of IgE antibody production. Immun. Rev. 1978; 41: 77-108.
20. Lakin JD, Strong MD, Sell KW. Polymyxin-B reactions, IgE antibody, and T-cell deficiency. Immunochemical studies in a patient after bone marrow transplantation. Ann. Int. Med. 1975; 83: 204-207.

CHAPTER 9

CEFTAZIDIME MONOTHERAPY FOR LOCALIZED INFECTIONS IN NEUTROPENIC PATIENTS. *

C. VERHAGEN*, B.E. DE PAUW*, TH. DE WITTE*, I. NOVAKOVA*, K.J. WILLIAMS+ and TH. BOTHOF**.

* Department of Hematology, University Hospital St Radboud, Nijmegen, The Netherlands
\+ Glaxo Group Research Ltd , Greenford, United Kingdom
Present address, ICI Pharmaceuticals, Alderly Park, Macclesfield Cheshire, UK
** Glaxo BV, Nieuwegein, the Netherlands

* **(Submitted to Archives of Internal Medicine).**

SUMMARY

A retrospective analysis of the results of ceftazidime monotherapy (CAZ) for 284 febrile episodes in neutropenic patients is presented. For infections with a known focus the clinical cure rate of secondary septicemia (S-SEP) was 73% (n=47); of the upper respiratory tract infections (URTI) 94% (n=29) and of the lower respiratory tract infections (LRTI) 84% (n=76) with monotherapy. The results in skin and soft tissue infections (SSTI) and in urinary tract infections (UTI) were 65% (n=23) and 88% (n=8) respectively. Only in SSTI was modification of therapy necessary significantly more often than in infections without clinical focus (p 0.01). Patients with localized infections required prolonged treatment in comparison to patients with fever of unknown origin or primary septicemia: a mean of 11 days compared to a mean of 9 days ($p<0.0001$). Despite a rising incidence of Gram-positive infections in neutropenic patients in general, the majority of pathogens in bacteriologically proven LRTI and UTI remained Gram-negative (66 and 80% respectively), whereas the overall incidence of Gram-negative infections was 44% in this study. Systemic mycotic infections were mainly associated with URTI (34%) and LRTI (21%). It is concluded that CAZ is an effective drug for the empiric treatment of febrile neutropenic patients with a localized infection, though subsidence of signs and symptoms takes longer than in patients without focus.

INTRODUCTION

Profound alterations in the host defences of cancer patients, due to the underlying malignancy or secondary to aggressive myelosuppressive therapy, have increased the risk and severity of infectious complications. Early mortality in febrile neutropenic patients has been reduced mainly by prompt institution of broadspectrum antibiotics. After the introduction of the combined use of an aminoglycoside with carboxypenicillin, the therapeutic armamentarium has been expanded and regimens of either a beta-lactam with an aminoglycoside or a double betalactam combination have been tested in clinical trials during the last decade. In addition to extension of antimicrobial spectrum, higher levels of serun bactericidal activity have been achieved accompanied by a better clinical outcome if the antimicrobial agents acted synergistically in the combination (1,2). Overall efficacy rates of 49-80% have been demonstrated in these patients. However, less favourable reponses were obtained in localized infections: cure rates of 23-63% in lower respiratory tract infections and 0-71% in secondary septicemia have been reported (3-12).

The newly developed third-generation cephalosporins have a broad spectrum of activity. Although less active in vitro against Gram-positive microorganisms than earlier compounds, they show remarkable activity against Gram-negative pathogens (13). With ceftazidime alone serum levels exceeding 40-250 times the minimum bactericidal concentration of most Gram-negative bacteria could be achieved in neutropenic patients (14-16), offering the possibility of monotherapy (17,18) which would avoid the toxicity (19,20) of various combination schedules (6,8,21,22).

We have assessed the role of ceftazidime monotherapy in several prospective randomized trials and the results compared favourably to established combination schedules (23-26). Analysis of *Pseudomonas aeruginosa* septicemia's in these patients showed that the cure rate was unaltered in localized infections, but patients with primary septicemia only had a faster resolution of symptoms and needed a shorter duration of therapy than those with septicemia secondary to a known focus (27). This retrospective analysis was performed to define the possible role of ceftazidime monotherapy in neutropenic patients with localized infections.

PATIENTS AND METHODS

Between January 1981 and January 1986 four clinical trials were conducted in order to assess the efficacy and safety of ceftazidime monotherapy in febrile neutropenic patients (23-26).All febrile episodes treated with ceftazidime monotherapy, in which a localized infection was demonstrated at that time have now been reanalyzed separately. Entry criteria, pretreatment evaluation, and follow up for the trials have been described previously (24). The empiric therapy was evaluated at 72 hours and modified only if the patient did not respond clinically, unless adverse reactions, isolation of a pathogen resistant to ceftazidime, or a deteriorating clinical status urged an earlier change of therapy. Therapy was in general continued until the patient was free of symptoms of infection for 4 days, or 2 days in cases when the granulocyte count increased to over $1000/mm^3$.

Upper respiratory tract infection (URTI) was diagnosed in cases where the patient had fever, complained of a sore throat or mouth, and showed signs of mucositis not related to previous cytotoxic treatment. Sinusitis and otitis media were included in this group of patients. The diagnosis of lower respiratory tract infection (LRTI) was based on the presence of fever, and at least one of the symptoms: cough, sputum production, dyspnoea and/or physical signs of pulmonary consolidation or a positive chest X-ray. Patients with fever and local tendernes, swelling or erythema, sometimes fluctuation, exsudation or ulceration as clinical manifestation of an infection of the skin or underlying tissues were diagnosed as skin and soft tissue infection (SSTI). All patients with fever and positive urine cultures ($>10^5$ microorganisms/ml) were considered to have an urinary tract infection (UTI). The clinical and bacteriological responses of these infections were compared to the results of the treatment of infections without a focus for all patients entered into the above mentioned randomised trials.

Antibiotic responses were clinically classified as: (a) "success", if all clinical signs and symptoms subsided without evidence of infection or recrudescence of fever at the time ceftazidime was discontinued, nor during follow up; (b) "success with modification", if ceftazidime was continued but resolution of infection occurred only after addition of other agents; (c) "failure" if there was no clinical response to ceftazidime alone, nor after treatment modification or death occurred within 72 hours; (d) "unassessable" classified were all those cases which proved to be viral

or fungal infections or in case fever was proven to be of non-infectious origin. Microbiological responses were defined as: (a) "success", if the original causative organism was eradicated by ceftazidime alone; (b) "success with modification", if only after additional treatment the original causative organism could be eradicated; (c) "failure" if cultures remained positive despite modification of therapy; (d) "unassessable" cases were as mentioned in the clinical definition supplemented by those for which no organism could be isolated. Any infection by a microorganism occurring during treatment, not recognized as the initially causative organism and requiring treatment, was defined as superinfection. New isolates without apparent signs of infection were defined as colonizations.

RESULTS

From 1981 until 1986, ceftazidime monotherapy was empirically instituted in 284 patients. The underlying disease was a hematological malignancy in the majority of patients (83%); 14% of the total developed fever during bone marrow transplantation. More males (161) than females (123) were allocated to ceftazidime monotherapy during this period. Other details are shown in Table I.

Tabel I

Ceftazidime Monotherapy in Neutropenia; Clinical Data.

Parameter		
No. of patients (male/female)		284 (161/123)
Mean age ± Standard deviation, (range) years		41.1 ± 16.5 (14-75)
Underlying disease (No of patients (%):		
	Acute leukemia	189 (67%)
	Myeloproliferative syndrome	47 (17%)
	Malignant lymphoma	12 (4%)
	Aplastic anemia	15 (5%)
	Solid tumor	20 (7%)
	(During bone marrow transplantation	41 -)
Infection localization:		
-Without Focus:	Fever of Unknown Origin	81 (29%)
	Primary Septicemia	77 (27%)
-With Focus*:	Upper Respiratory Tract Infection	29 (10%)
	Lower Respiratory Tract Infection	76 (27%)
	Skin and Soft Tissue Infection	23 (8%)
	Urinary Tract Infection	8 (3%)
	(Secondary Septicemia	47 -)
* No of patients with two separate infection sites		10 -

Thirty-six out of 284 patients were considered to be unassessable due to mycotic (24) and viral infections (4), tuberculosis (2) and other reasons (6) (Table II).

Tabel II

Unassessable Patients

Origin fever	No Focus FUO	No Focus P-SEP	Focal site URTI	Focal site LRTI	Total patients
Tuberculosis	1 (1)*			1	2 (1)
Fungal infection		1	10+	16 (9)+	24 (9)+
Viral infection		2 (1)	1	1	4 (1)
Drug fever**	5				5
Total body iradiation	1				1
Total unassessable	7 (1)	3 (1)	11+	18 (9)+	36 (11)+

FUO = Fever of Unknown Origin, P-SEP = Primary septicemia, URTI = Upper Respiratory Tract Infection, LRTI = Lower Respiratory Tract Infection.

* (No.) unassessable patients who died.
\+ Three of the systemic mycotic infections were localized in the upper and lower respiratory tract.
** Attributed to earlier instituted cephaloridine gargle (1), cytarabinoside (1), and anti-thymocyte globuline (3)

The clinical cure rate of ceftazidime monotherapy in the 248 assessable patients was 201 (81%). Thirty-five patients (14%) improved after modification of therapy and 12 patients (5%) failed despite modification. Bacteriological eradication was achieved in 133 (82%) out of 163 strains treated with ceftazidime alone. A localized infection with or without a septicemia was diagnosed in 126 out of 284 patients. Foci of infection were URTI in 29 (21%), LRTI in 76 (56%), SSTI in 23 (17%) and UTI in 8 (6%) patients. Ten patients had more than one localized infection at the onset of fever, and 47 developed bacteremia secondary to a known focus. Table III shows the details of the clinical infections. Relatively more males than females suffered a localized infection compared with the ratio in patients without known focus. This difference was significant for LRTI ($p<0.05$). The mean age of patients with LRTI and UTI (47 and 46 yrs.) was higher than that of patients with an URTI (34 yrs.). LRTI accounted for 48% of all infections in patients over 60 years which was 5 times the incidence of bronchopneumonia in the age group of less than 20 years. In contrast, URTI mainly occurred under 30 years of age.

Table III

Clinical data and Results of Therapy in Localized Infections*

Results	FUO	P-SEP	S-SEP	URTI	LRTI	SSTI	UTI
No of patients(male/female)	81 (40/41)	77 (39/38)	47 (32/15)	29 (16/13)	76 (50/26)	23 (16/7)	8 (5/3)
Mean age (range) years	40 (16-74)	39 (15-72)	40 (15-70)	34 (15-69)	47 (15-75)	40 (16-68)	46 (30-68)
Isolated pathogens							
None	80 (99%)	-	-	3 (10%)	21 (28%)	6 (26%)	-
Single pathogen	1 (1%)+	72 (94%)	32 (68%)	20 (69%)	44 (58%)	12 (52%)	6 (75%)
Multiple pathogens	-	5 (6%)	15 (32%)	6 (21%)	11 (14%)	5 (22%)	2 (25%)
Secondary septicemia**	-	-		13 (45%)	24 (32%)	12 (52%)	5 (63%)
Clinical cure overall	67 (82%)	54 (70%)	29 (62%)	17 (59%)	47 (62%)	15 (65%)	7 (88%)
No of assessable patients	74	74	40	18	58	23	8
Clinical cure	67 (91%)	54 (73%)	29 (73%)	17 (94%)	47 (84%)	15 (65%)	7 (88%)
Cure with modification	7 (9%)	11 (15%)	11 (27%)	1 (6%)	8 (11%)	8 (35%)	1 (12%)
Failure	-	9 (12%)	-	-	3 (5%)	-	-
No of isolates	-	82	56	19	47	23	10
Bacteriological success		61 (74%)	44 (79%)	17 (89%)	44 (94%)	16 (70%)	9 (90%)
Success with modification		12 (15%)	12 (21%)	2 (11%)	3 (6%)	7 (30%)	1 (10%)
Failure		9 (11%)	-	-	-	-	-

FUO = Fever of Unknown Origin, P-SEP = Primary Septicemia, S-SEP = Secondary Septicemia, URTI = Upper Respiratory Tract Infection, LRTI = Lower Respiratory Tract Infection, SSTI = Skin and Soft Tissue Infection, UTI = Urinary Tract Infection.

* Total patients entered are 284; 10 patients had more than one localized infect and 47 patients had septicemia secondary to a localized infection, hence the total of the collums is 341.
+ Miliaire tuberculosis; post mortem diagnosis.
** Secondary septicemia occurred in 7 patients with more than one localized infection.

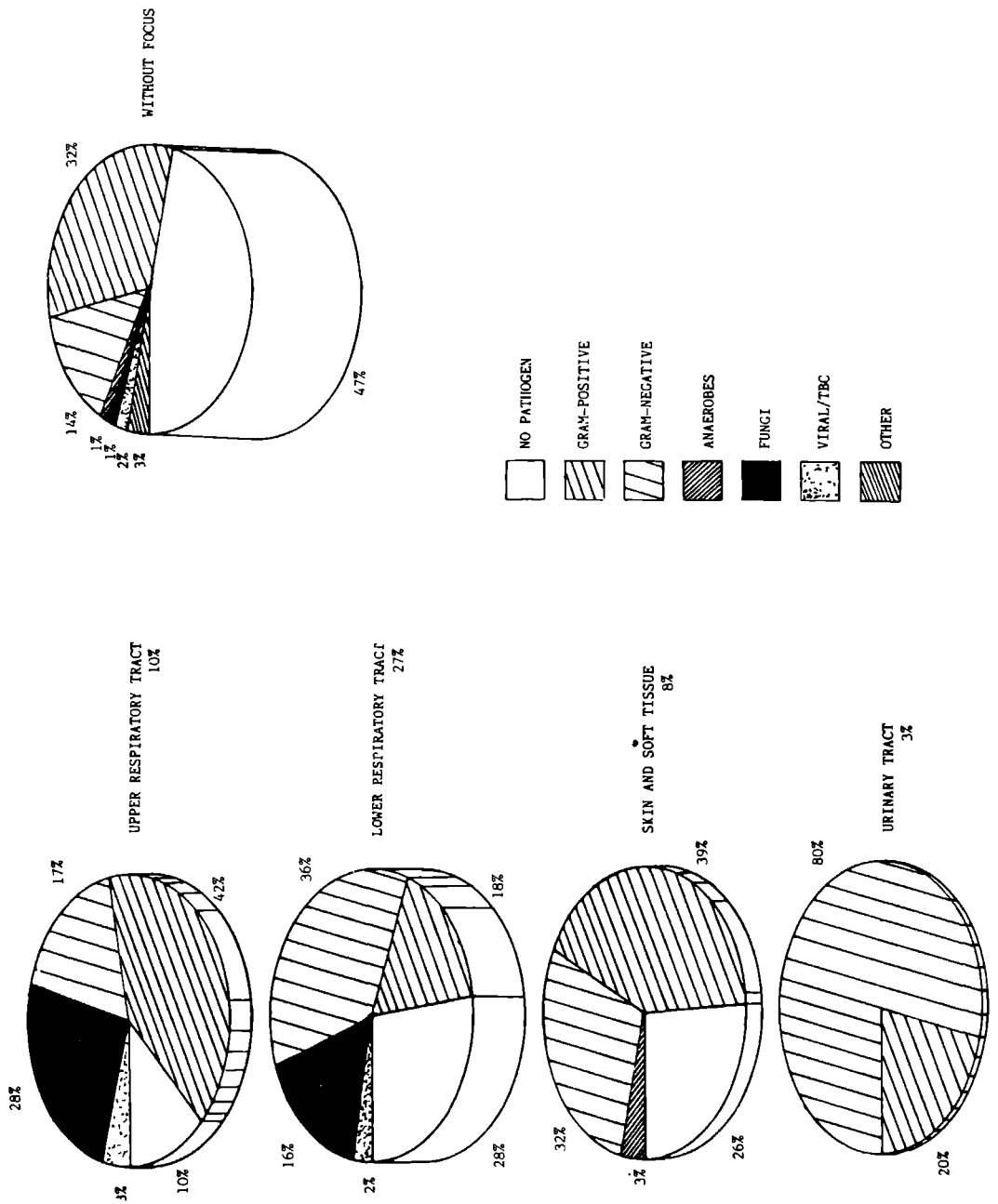
Clinically proven infections.

Clinical cure with ceftazidime monotherapy was achieved in 17 out of 29 (59%) patients with an URTI, in 47 out of 76 (62%) with LRTI, in 15 out of 23 (65%) with SSTI, and in 7 out of 8 (88%) with UTI. The overall clinical cure rate of the assessable cases with a localized infection was 80% (Table III). Modification of therapy was successful in all patients with URTI, SSTI, and UTI. Failures occurred in 3 out of 58 (5%) patients with LRTI. One patient with a pneumonia, caused by *Klebsiella pneumoniae* and *Escherichia coli*, died on the 4th day of treatment of a myocardial infarction; postmortem cultures appeared to be negative. The other 2 patients died, on the 8th and 21th day of treatment respectively, in spite of salvage therapy with amikacin and amphotericin-B. During the course of the disease no pathogens were isolated.

Microbiologically proven infections.

The infective agent was isolated from all 8 UTI cases and from 90% of the

FIGURE 1
INCIDENCE OF PATHOGENS IN 284 NEUTROPENIC PATIENTS
INFECTIONS WITH AND WITHOUT FOCUS.



29 URTI cases. In LRTI and SSTI cultures were positive in less than 75% of the cases. Multiple pathogens were isolated more frequently from patients with localized infections than from patients with a primary septicemia ($p < 0.05$, Table III). Figure 1 and Table IV show the distribution of the microorganisms in localized infections. The majority of infections in URTI were caused by Gram-positive bacteria, followed by fungi as the second major pathogen. In contrast, Gram-negative microorganisms were twice as frequently isolated in LRTI than Gram-positive pathogens or fungi. Also in UTI the majority of pathogens were Gram-negative. In SSTI both Gram-positive and Gram-negative organisms were evenly involved as causative pathogen. The bacteriological clearance rate for assessable patients was 95% in URTI, 90% in LRTI, 70% in SSTI, and 90% in UTI.

Tabel IV

Distribution of Pathogens in Localized Infections and Results of Therapy.

Organism	P-SEP		URTI		LRTI		SSTI		UTI		Total*	
	S	F	S	F	S	F	S	F	S	F	S	F
Gram-positive microorganism	39	16	13	1	8	4	6	6	1	1	64	26
Staphylococcus epidermidis	11	7	3	1	5	3	3	2	–	–	21	12
Staphylococcus aureus	8	3	2	–	1	–	2	2	1	–	13	5
Streptococcus viridans	15	–	3	–	2	–	1	–	–	–	20	–
Beta-haemolytic *streptococci*	2	–	4	–	–	–	–	–	–	–	6	–
Streptococcus sanguis	3	2	1	–	–	–	–	–	–	–	4	2
Streptococcus faecalis	–	1	–	–	–	–	–	2	–	1	–	3
Streptococcus pneumoniae	–	1	–	–	–	–	–	–	–	–	–	1
Corynebacterium parvum	–	2	–	–	–	–	–	–	–	–	–	2
Diphtheroids	–	–	–	–	–	1	–	–	–	–	–	1
Gram-negative microorganisms	23	2	5	–	30	–	10	–	8	–	69	2
Pseudomonas aeruginosa	8	–	3	–	13	–	5	–	4	–	30	–
Escherichia coli	5	2	–	–	1	–	2	–	–	–	8	2
Klebsiella species	4	–	–	–	5	–	–	–	–	–	9	–
Haemophilus influenzae	3	–	1	–	5	–	–	–	–	–	8	–
Enterobacter cloacae	–	–	1	–	4	–	2	–	2	–	7	–
Proteus mirabilis	1	–	–	–	1	–	1	–	1	–	3	–
Campylobacter species	2	–	–	–	–	–	–	–	–	–	2	–
Acinetobacter species	–	–	–	–	–	–	–	–	1	–	1	–
Citrobacter freundii	–	–	–	–	1	–	–	–	–	–	1	–
Anaerobic microorganisms	–	1	–	–	–	–	–	1	–	–	–	2
Clostridium perfringens	–	1	–	–	–	–	–	–	–	–	–	1
Anaerobic species	–	–	–	–	–	–	–	1	–	–	–	1

P-SEP = Primary septicemia, URTI = Upper Respiratory Tract Infection, LRTI = Lower Respiratory Tract Infection, SSTI = Skin and Soft Tissue Infection, UTI = Urinary Tract Infection, S = Success, F = Failure

* Organisms isolated from more than one localized infection in the same patient were counted once in the collum "Total".

Table V

Granulocytes Before Treatment and at Time of Response*

Neutrophils	Fever without Focus Start	Fever without Focus Response	Localized Infection Start	Localized Infection Response
< 250/mm³	104 (66%)	73 (60%)	76 (61%)	34 (42%)
250- 500/mm³	29 (18%)	33 (27%)	23 (18%)	26 (33%)
501-1000/mm³	23 (15%)	9 (8%)	20 (16%)	15 (19%)
> 1000/mm³	2 (1%)	6 (5%)	7 (5%)	5 (6%)

* For successfully treated patients

Sixty-four percent of all febrile patients had less than 250 granulocytes/mm at the start of treatment. At the time of response 95% still had less than 1000 granulocytes/mm^3 (Table V).

Duration of treatment was recorded in all successfully treated patients as well as the time to resolution of pyrexia and symptoms (Table VI). In patients without a focus of infection, the mean duration of treatment was 8.9 days with a range from 5 to 20 days, the mean time before normalization of the temperature was 3.6 days and before resolution of symptoms 2.9 days. The patients with localized infections in general required longer treatment with a mean of 11.1 days (6 ± 51, $p < 0.0001$). Likewise a longer persistance of pyrexia was observed with a mean of 4.6 days ($p < 0.0001$) and a mean of 5.4 days before resolution of symptoms occurred ($p < 0.0001$). An exception were the patients with UTI, they had a quick resolution of pyrexia (3 days) and symptoms (2.3 days).

Tabel VI

Duration of Therapy, Fever and Symptoms in Localized infections

Infection	Therapy (days)*	p**	Fever (days)*	p**	Symptoms (days)*	p**
No focus	8.9 ± 3.0 (5-20)		3.6 ± 1.7 (1-17)		2.9 ± 1.9 (1- 9)	
FUO	8.7 ± 3.2 (5-20)		3.4 ± 1.5 (1- 7)		2.7 ± 1.8 (1- 9)	
P-SEP	9.2 ± 2.7 (5-17)		3.8 ± 2.0 (5-17)		3.1 ± 2.1 (1- 9)	
With focus	11.1 ± 5.6 (6-51)	p<0.0001	4.6 ± 2.8 (1-16)	p<0.0001	5.4 ± 4.0 (1-40)	p<0.0001
S-SEP	11.3 ± 5.7 (6-31)	p<0.003	4.7 ± 3.3 (2-15)	p<0.005	5.2 ± 4.2 (1-17)	p<0.0001
URTI	8.8 ± 2.7 (6-15)	ns	3.9 ± 1.4 (2- 6)	p<0.03	4.2 ± 1.3 (2- 7)	p<0.0001
LRTI	11.1 ± 4.9 (6-31)	p<0.0001	4.7 ± 3.1 (1-15)	p<0.0004	5.8 ± 3.5 (2-17)	p<0.0001
SSTI	13.3 ± 10.7 (7-51)	p<0.006	5.5 ± 3.6 (2-16)	p<0.003	6.5 ± 10.3 (1-40)	p<0.002
UTI	10.3 ± 4.1 (9-19)	ns	3.0 ± 2.1 (1- 8)	ns	2.3 ± 0.9 (1- 3)	ns

* mean ± standard deviation and (range).
** Wilcoxon test.

FUO = Fever of Unknown Origin, P-Sep = Primary Septicemia, S-SEP = Secondary Septicemia, URTI = Upper Respiratory Tract Infection, LRTI = Lower Respiratory Tract Infection, SSTI = Skin and Soft Tissue Infection, UTI = Urinary Tract Infection.

DISCUSSION

At initiation of therapy, localized infections could be found in 44% of the patients. The overall clinical cure was substantially inferior in upper and lower respiratory tract infections in comparison to all other cases. Analysis showed that this difference may be explained by an increased incidence of fungal infections. Clinical cure rates in assessable patients with and without a clinical focus were similar. In contrast to the increasing incidence of Gram-positive infections in immunocompromised patients, which has been reported in the literature repeatedly (28-30), the majority of infections in patients with LRTI and UTI were caused by Gram-negative pathogens. Sickles (31) in 1973 and Bodey (32) in 1978 reported the same high incidence of Gram-negative pathogens in LRTI; hence a shift of causative pathogens in these infections during the last decenium seems less obvious. Except for fungal infections in URTI, the distribution of Gram-positive and negative organisms was equal in both URTI and SSTI. Patients with pharyngitis were mainly affected by streptococci susceptible to ceftazidime. In SSTI the major infecting pathogen proved to be Enterococcus *faecalis*, which is never sensitive to ceftazidime, or *Staphylococcus epidermidis*. The latter was mainly associated with intravenous lines and about half of the strains were sensitive to ceftazidime. Patients with SSTI needed modification of therapy more frequently (35%), ($p < 0.01$), whereas the majority of assessable patients with URTI, LRTI and UTI were cured by ceftazidime alone.

The efficacy of aminoglycosides, especially when tissue invasion occurs, is questionable. Only the use of synergistic combination treatment may circumvent this problem (33). From the present study it appeared that the efficacy of ceftazidime to eradicate a pathogen was not influenced by tissue localization of an infection; bacteriological clearance was usually achieved when the isolated organism demonstrated in vitro sensitivity. Although the eventual cure rates of localized and non-localized infections were similar, some obvious differences were observed. The time elapsed between the start of treatment and subsidence of symptoms appeared to be prolonged in patients with an infectious focus. A larger bacterial load in these infections could be an explanation, since the penetration of ceftazidime in the different tissues has been shown to reach adequate bactericidal levels (34,35). Treatment with a synergistic combination, including ceftazidime, may shorten the duration of illness and,

Table VII

Empiric Therapy of Localized Infections in the Neutropenic Host

Antibiotic(s)	Reference(s)	N	Total	FUO	P-SEP	S-SEP	URTI	LRTI	SSTI	UTI
Aminoglyc. + pen.	4,6,10-12	1137	61%	59%	73%	39%	86%	45%	77%	92%
Aminoglyc. + ceph.	5,7,12	285	64%	63%	74%	-	-	57%	62%	100%
Double beta-lactam	3,6,9	788	59%	63%	72%	44%	83%	36%	62%	88%
Monobactam + vanco	9	100	68%	67%	86%	-	-	42%	80%	100%
Penicillin + vanco	8	193	65%	60%	78%	-	-	37%	71%	100%
Ceftazidime alone	23-26 (this study)	284	81%	91%	74%	73%	94%	84%	65%	88%

FUO = Fever of Unknown Origin, P-SEP = Primary Septicemia, S-SEP = Secondary Septicemia, URTI = Upper Respiratory Tract Infection, LRTI = Lower Respiratory Tract Infection, SSTI = Skin and Soft Tissue Infection, UTI = Urinary Tract Infection, Aminoglyc = aminoglycoside, pen = penicillin, ceph = cephalosporin, vanco = vancomycin.

consequently, the length of treatment required in patients with localized infections. This hypothesis however, needs corroboration in a prospective study and has to be weighed against the possibly higher toxicity of such a combination.

Ten out of 12 (83%) URTI and 16 out of 29 (55%) LRTI which failed empirical ceftazidine monotherapy proved to be associated with a fungal infection. More than half of the mycotic LRTI were fatal despite systemic antifungal therapy. Early diagnosis of mycotic infections in these patients is difficult. Neither serology, nor culturing proved to be reliable indicators of fungal invasion (36,37). Early empirical institution of systemic antifungal therapy may be beneficial especially in patients with URTI and LRTI not improving on initially instituted anti-bacterial therapy.

It may be stated that empirically instituted ceftazidime monotherapy is a safe and well tolerated strategy in febrile neutropenic patients with a localized infection. Its efficacy is not hampered by localization of the infection and the results obtained compare favourably with established combinations especially in LRTI (Table VII). The addition of a specifically anti-staphylococcal compound in patients suspected of a catheter associated infection may be beneficial. Early systemic antifungal therapy should be considered in case empirical monotherapy fails in LRTI or URTI.

REFERENCES

1. Klastersky J: Empiric treatment of infections in neutropenic patients with cancer. Rev. Inf. Dis. 1983; 5S: 21-31.
2. Klastersky J, Glauser MP, Schimpff SC, et al: Prospective randomized comparison of three antibiotic regimens for empiric therapy of suspected bacteremic infections in febrile granulocytopenic patients. Antimicrob. Ag. Chemother. 1986; 29: 263-270.
3. Bodey GP, Valdivieso M, Feld R, et al: Carbenicillin plus cephalothin or cefazolin as therapy for infections in neutropenic patients. Am. J. Med. Sci. 1977; 273: 309-318.
4. Bodey GP, Ketchel SJ, and Rodriguez V.: A randomized study of carbenicillin plus cefamandole or tobramycin in the treatment of febrile episodes in cancer patients. Am. J. Med. 1979; 67: 608-616.
5. Fainstein V, Bodey GP, Elting L, et al: A randomized study of ceftazidime compared to ceftazidime and tobramycin for the treatment of infections in cancer patients. J. Antimicrob. Chem. 1983; 12 Suppl. A: 101-110.
6. Fainstein V, Bodey GP, Bolivar R, et al: Moxalactam plus ticarcillin or tobramycin for treatment of febrile episodes in neutropenic cancer patients. Arch. Intern. Med. 1984; 144: 1766-1770.
7. Feld R, Rachlis A, Tuffnell PG, et al: Empiric therapy for infections in patients with granulocytopenia. Arch. Intern. Med. 1984; 144: 1005-1010.
8. Jadeja L, Bolivar R, Fainstein V, et al: Piperacillin plus vancomycin in the therapy of febrile episodes in cancer patients. Antimicrob. Ag. Chemother. 1984; 26: 295-299.
9. Jones P, Rolston K, Fainstein V, et al: Aztreonam plus vancomycin (plus amikacin) vs. moxalactam plus ticarcillin for the empiric treatment of febrile episodes in neutropenic cancer patients. Rev. Inf. Dis. 1985; 7 Suppl. 4: 741-746.
10. De Jongh CA, Wade JC, Schimpff SC, et al: Empiric antibiotic therapy for suspected infection in granulocytopenic cancer patients. Am. J. Med. 1982; 73: 89-96.
11. Keating MJ, Bodey GP, Valdivieso M, and Rodriguez V: A randomized comparative trial of three aminoglycosides- comparison of continuous infusions of gentamicin, amikacin, and sisomicin combined with carbenicillin in the treatment of infections in neutropenic patients with malignancies. Medicine 1979; 58: 159-170.
12. Lawson RD, Gentry LO, Bodey GP, et al: A randomized study of tobramycin plus ticarcillin, tobramycin plus cephalothin and ticarcillin or tobramycin plus mezlocillin in the treatment of infections in neutropenic patients with malignancies. Am. J. Med. Sci. 1984; 287: 16-23.
13. Rolinson GN: Beta-lactam antibiotics. J. Antimicrob. Chem. 1986; 17: 5-36.
14. Verbist L, and Verhaegen J: Ceftazidime: comparative in-vitro study. J. Antimicrob. Chem. 1981; 8 Suppl. B: 67-71.
15. Knothe H, and Dette GA: The in-vitro activity of ceftazidime against clinically important pathogens. J. Antimicrob. Chem. 1981; 8 Suppl. B: 33-41.
16. Standiford HC, Drusano GL, Fitzpatrick B, et al: Bactericidal activity of ceftazidime in serum compared with that of ticarcillin combined with amikacin. Antimicrob. Ag. Chemother. 1984; 26: 339-342.

17. Pizzo PA, Hathorn JW, Hiemenz J, et al: A randomized trial comparing ceftazidime alone with combination antibiotic therapy in cancer patients with fever and neutropenia. N. Eng. J. Med. 1986; 315: 552-558.
18. Fainstein V, and Bodey GP: Single-agent therapy for infections in neutropenic cancer patients. Am. J. Med. 1985; 79 Suppl. 2A: 83-88.
19. Meyers BR: Comparative toxicities of third-generation cephalosporins. Am. J. Med. 1985; 79 Suppl. 2A: 96-103.
20. Verhagen C, De Pauw BE, De Witte T, et al: Ceftazidime does not enhance cyclosporin-A nephrotoxicity in febrile bone marrow transplantation patients. Blut 1986; 53: 333-339.
21. Bodey GP, Rodriguez V, Valdivieso M, and Feld R: Amikacin for treatment of infections in patients with malignant diseases. J. Infect. Dis. 1976; 134: s421-s427.
22. Winston DJ, Ho WG, Young LS, et al: Piperacillin plus amikacin therapy versus carbenicillin plus amikacin therapy in febrile granulocytopenic patients. Arch. Int. Med. 1982; 142: 1663-1667.
23. De Pauw BE, Kauw F, Huytjens M, et al: Randomized study of ceftazidime versus gentamicin plus cefotaxime for infections in severe granulocytopenic patients. J. Antimicrob. Chemother. 1983; 12 Suppl. A: 93-99.
24. De Pauw BE, Williams K, De Neeff J, et al: A randomized prospective study of ceftazidime versus ceftazidime plus flucloxacillin in the empiric treatment of febrile episodes in severely neutropenic patients. Antimicrob. Ag. Chem. 1985; 28: 824-828.
25. De Pauw BE, Bothof T, Williams K, et al: A randomized study of ceftazidime versus ceftazidime plus cephalothin in febrile neutropenic patients. 14th Intern Conf Chemother, Kyoto 1985 S.P52 abstr. 54.
26. Verhagen C, De Pauw BE, Janssen JThP, et al: A prospective randomized study of ceftazidime sodium versus ceftazidime arginine in febrile neutropenic patients. IXth Int Conf Infect Parasitic Dis Munich 1986; abstr. 779.
27. Verhagen C, De Pauw BE, Donnelly JP, et al: Ceftazidime alone for treating *Pseudomonas aeruginosa* septicaemia in neutropenic patients. J. Infection 1986; 13: 125-131.
28. Pizzo PA, Ladisch S, Simon RM, et al: Increasing incidence of Gram-positive sepsis in cancer patients. Med. Ped. Oncology 1978; 5: 241-244.
29. Young LS. Nosocomial infections in the immunocompromised adult. Am. J. Med. 1981; 70: 398-404.
30. Wade JC, Schimpff SC, Newman KA, and Wiernik PH: *Staphylococcus epidermidis*: An increasing cause of infection in patients with granulocytopenia. Ann. Int. Med. 1982; 97: 503-508.
31. Sickles EA, Young VM, Greene WH, and Wiernik PH: Pneumonia in acute leukemia. Ann. Int. Med. 1973; 79:528-534.
32. Bodey GP, Rodriguez V, Chang HY, and Narboni G: Fever and infection in leukemic patients: A study of 494 consecutive patients. Cancer 1978; 41: 1610-1622.
33. Bodey GP: Antibiotics in patients with neutropenia. Arch. Intern. Med. 1984; 144: 1845-1851.
34. Walstad RA, Hellum KB, Blika S, et al: Pharmacokinetics and tissue penetration of ceftazidime: studies on lymph, aqueous humour, skin blister, cerebrospinal and pleural fluid. J. Antimicrob. Chem. 1983; 12 Suppl. A: 275-282.

35. Adam D, Reichart B, and Williams KJ: Penetration of ceftazidime into human tissue in patients undergoing cardiac surgery. J. Antimicrob. Chem. 1983; 12 Suppl. A: 269-273.
36. Aisner J, Stephen C. Schimpff C, and Wiernik PH: Treatment of invasive aspergillosis: Relation of early diagnosis and treatment to response. Ann. Int. Med. 1977; 86: 539-543.
37. Singer C, Kaplan MH, and Armstrong D: Bacteremia and fungemia complicating neoplastic disease: A study of 364 cases. Am. J. Med. 1977; 62: 731-742.

CHAPTER 10

SUMMARY SAMENVATTING

TREATMENT OF BACTERIOLOGICAL INFECTIONS IN NEUTROPENIC PATIENTS WITH SPECIAL EMPHASIS ON CEFTAZIDIME MONOTHERAPY.

Chapter 1 An introduction is given to infectious complications in the immunocompromised host. Retrospective analysis of all patients with acute leukemia admitted between 1972 and 1985 at the St. Radboud Hospital (Nijmegen) has shown an infection related mortality of 50%. Prevention, diagnosis and possible treatment modalities have been discussed. The attention was focussed on empiric monotherapy with ceftazidime in febrile neutropenic patients.

Chapter 2 An outline of the studies performed and their specific objectives are given.

Chapter 3 In an earlier study ceftazidime monotherapy has proven to be significantly more effective for the treatment of febrile neutropenic patients than gentamicin plus cefotaxime. However, in case of infections caused by Gram-positive pathogens, ceftazidime is less effective than "earlier generations" of cephalosporins. The combination of ceftazidime plus cephalothin is compared with ceftazidime alone in a prospective randomized trial for empiric treatment of 102 febrile neutropenic patients. A cure of 72% has been achieved in both arms of the study. The combination proves to be slightly more effective, though not significant, in case of staphylococcal infections. When necessarily, vancomycin has been added after 48 to 72 hrs. The ultimate outcome is not affected by this delay and does not warrant earlier empiric institution of a more broad spectrum and possibly more toxic combination.

Chapter 4 In this chapter we compare the the efficacy and safety of a new formulation of ceftazidime (CAZ) "CAZ-arginine" (CAZ-ARG) with the marketed blend of CAZ sodium (CAZ-S). The latter is known for its practical drawback, on disolving it may generate many small non toxic bubbles in the infusion lines. CAZ-ARG lacks this disadvantage. The clinical cure rate for

100 febrile neutropenic patients treated in this prospective randomized trial is 91% (CAZ-S) and 83% (CAZ-ARG). Bacteriological clearance has been achieved in 87% for CAZ-S and 81% for CAZ-ARG respectively. The nurses in the ward preferes CAZ-ARG being easier to handle and less time consuming to prepare. No difference in efficacy or safety of both formulations has been found.

Chapter 5 Although ceftazidime monotherapy proves to be effective in the majority of febrile neutropenic patients, still a minority with infections due to Gram-positive microorganisms need modification. In this chapter we report the results of a pilot study about the efficacy and safety of teicoplanin, a new glycopeptide antibiotic related to vancomycin, as modification therapy in case of failure after initial empiric ceftazidime monotherapy. Teicoplanin is easy to apply (once daily push injection intravenously of 200 mg), and has been chosen for a possible lack of nephrotoxicity and ototoxicity. Twenty patients are included in this study. Clinical cure is achieved in 11 out of 16 assessable cases (69%), and 10 out of 11 (91%) bacteriologically confirmed infections has been cured after addition of teicoplanin. No nephrotoxicity or ototoxicity is encountered, but 4 patients has shown a transient rise in liver transaminases. There is a large interindividual variation in serum levels attained and the mean through level remaines below the MIC 90 of staphylococci until day 7 of therapy. Provisional figures of an ongoing study with higher daily dosis of teicoplanin may suggest an increased chance on hepatotoxicity and ototoxicity. The question of a safe and reliable dosing schedule renains open, although the efficacy of teicoplanin in this small group neutropenic patients with infections due to Gram-positive pathogens has been shown.

Chapter 6 Any empiric therapy in neutropenic patients must provide evidence of efficacy in Gram-negative infections. The efficacy of ceftazidime monotherapy has been reviewed for *Pseudomonas aeruginosa* septicemia in neutropenic patients. Bacteriological clearance has been achieved in all by ceftazidime alone. Only 1 out of 29 patients died due to a cerebral hemhorhage on the 6th day of treatment. In localized infections subsidence of pyrexia and symptoms has taken longer than in patients with primary septicemia, although the eventual outcome has not been hampered in case secondary septicemia did occur.

Chapter 7 Patients undergoing allogeneic bone marrow transplantation are treated empirically with ceftazidime monotherapy in case fever occurs. No enhancement of the well known nephrotoxicity of cyclosporin-A is observed during therapy. The overall clinical cure rate of ceftazidime alone in these patients is 72%, bacteriological clearance is achieved in 63% only, due to the higher incidence of resistant Gram-positive microorganisns in these patients. We conclude that ceftazidime monotherapy is a safe alternative for potentially nephrotoxic combination regimens in the empiric treatment of febrile neutropenic patients treated concomitantly with cyclosporin-A, if one is prepared to modify therapy in case a resistant Gram-positive organisms is encountered.

Chapter 8 Drug related toxicodermia occurs frequently in patients with acute non lymphocytic leukemia. Drugs like allopurinol, co-trimoxazole, miconazole and ketoconazole are significantly more often associated with skinreactions during remission induction, than during maintenance therapy. Penicillin therapy is interrupted in 12% of these patients due to this complication. The overall incidence of skin reactions due to cephalosporins remaines low (3%, p 0.001) and only one patient has developed a rash related to ceftazidime.

Chapter 9 Localized infections responds less favourably to therapy than infections without known focus. On thorough examination 44% of the febrile neutropenic patients shows a localization of the infection. The distribution of pathogens is not the same for the different locations. Especially systemic fungal infections are mainly associated with infections of the tractus respiratorius. Gram-negative microorganisms are the major pathogen in urinary tract and lower tractus respiratorius infections, while Gram-positive pathogens are isolated more frequently in primary septicemia or skin and soft tissue infections. In the latter ceftazidime monotherapy does need modification significantly more often in order to cure the patient. Patients without focus responds faster with subsidence of symptoms and pyrexia than those with a proven focus of infection and needs less therapy to cure. Although the efficacy of ceftazidime to eradicate a pathogen is not hampered by tissue localization, synergistic combination therapy may be beneficial in case of a localized infection, but this hypothesis still needs confirmation.

Infection has been the major sole cause of mortality in patients with hematological diseases complicated by granulocytopenia during the past three decades. The incidence of infection related mortality is diminishing during the past 7 years in the St. Radboud hospital. Selective gut decontamination, early institution of therapy, experience developed during the past trials and last but not least the availabillity of potent antibiotics like ceftazidime may all have influenced this outcome. Ceftazidime has proven to be a reliable and less toxic alternative for the conventional combination regimens as empiric therapy for febrile neutropenic patients. Infections due to Gram-positive pathogens occurs more often in patients with skin and soft tissue tissue infections, during septicemia or after bone marrow transplantation. Ceftazidime is less effective against these pathogens, though an extension of the therapy step by step has been shown a safe alternative for initial broadspectrum combination therapy and may reduce additional costs and complications. Ceftazidime is expensive. But to compare the costs of combination therapy one must consider also the increase of associated workload, use of extra infusion sets, monitoring of serum levels and possible side effects, or treatment in case complications do occur, besides the extra costs of the chosen antibiotics.

DE BEHANDELING VAN BACTERIELE INFECTIES BIJ NEUTROPENISCHE PATIENTEN MET SPECIAAL AANDACHT VOOR MONOTHERAPY MIDDELS CEFTAZIDIME.

Hoofdstuk 1 Een inleiding in de problematiek van infecties bij patienten met granulocytopenie wordt gegeven. Uit retrospectief onderzoek blijkt dat 50% van de patienten met acute leukemie opgenomenin het St. Radboud ziekenhuis in de periode 1972-1985 is komen te overlijden ten gevolge van een infectie. Mogelijkheden ter preventie, opsporing en behandeling komen aan de orde. Hierbij wordt n.n. ingegaan op de vroegtijdige empirische behandeling van de granulocytopenische patient met koorts. Voor- en nadelen van de conventionele combinatie therapien worden besproken evenals de eerste resultaten van monotherapy met ceftazidime, een derde generatie cephalosporine.

Hoofdstuk 2 Hierin komen de verschillende vraagpunten aan de orde om de plaats van ceftazidime monotherapie bij een granulocytopenische patient met koorts nader te bepalen.

hoofdstuk 3 Uit een eerder verricht onderzoek is gebleken, dat ceftazidime monotherapie significant effectiever is dan de combinatie van gentamicine met cefotaxime bij de behandeling van de granulocytopenische patient met koorts. Echter bij infecties veroorzaakt door Gram-positieve microorganismen is ceftazidime minder werkzaam dan de eerdere generaties cephalosporinen. Dit hoofdstuk handelt over onderzoek naar de effectiviteit van de combinatie ceftazidime en cephalothin in vergelijking met die van ceftazidime alleen. Volgens een prospectief gerandomizeerde wijze zijn 102 patienten met de combinatie of monotherapie behandeld. In beide armen van de studie is een genezing bereikt bij 72% van de behandelde patienten. Alleen bij infecties veroorzaakt door staphylococcen lijkt de combinatie meer effectief zonder echter een statistische limiet van significantie te bereiken. Na 48 tot 72 uur is de behandeling met vancomycine uitgebreid voor die patienten die onvoldoende reageerden op de empirisch ingestelde therapie. De uiteindelijke genezing is hierdoor niet beinvloed. Uit de resultaten van dit onderzoek hebben wij geconcludeerd, dat toevoeging van cephalothin aan ceftazidime geen wezenlijke bijdrage vormt voor de

empirische therapie van de neutropenische patient met koorts en dat uitbreiding achteraf met een breedspectrum antie Gram-positief middel na falen van de initiele therapie de patient een mogelijk onnodige behandeling en eventuele bijwerkingen bespaart.

Hoofdstuk 4 De handelsvorm van ceftazidime is gemengd met natrium bicarbonaat om de oplosbaarheid te verbeteren. Een praktisch nadeel hiervan is de vorming van kooldioxide bij het oplossen, met als gevolg een toegenome druk in de flacon en de vorming van vele, zij het onschadelijke, kleine belletjes in de toevoerleidingen van het infuus. In een gecombineerd onderzoek met de verpleegkundige staf zijn wij de effectiviteit en veiligheid van een andere vorm van ceftazidime, een arginine verbinding, nagegaan. De effectiviteit bij 50 granulocytopenische patienten met koorts blijkt vergelijkbaar te zijn met die van het natrium zout. Voor de verpleegkundigen echter blijkt ceftazidime arginine een duidelijk voordeel door de afwezigheid van gasvorming bij gereedmaken van het infuus en daardoor minder verlies van tijd en materiaal dan bij verwerking van het conventionele preparaat.

Hoofdstuk 5 Ceftazidime alleen voldoet niet in een klein aantal patienten met infecties tgv. Gram-positieve organismen. Teicoplanin, een antibioticum verwant aan vancomycine, is op zijn waarde onderzocht als additionele behandeling bij falen van ceftazidime monotherapie. De mogelijk kleinere kans op nephro- en ototoxiciteit en eenvoud van toediening (1x daags intraveneuze injectie van 200 mg) hebben mede de keuze van dit middel bepaald. Aan 20 granulocytopenische patienten met persisterende koorts ondanks het gebruik van ceftazidime is teicoplanin aan de behandeling toegevoegd. Vier patienten zijn afgevallen daar achteraf blijkt, dat hun koorts niet door een Gram-positief organisme is veroorzaakt. Elf (69%) van de overige 16 patienten zijn genezen en 10 van de 11 geisoleerde microorganismen zijn geelimineerd. Gehoorsstoornissen of afwijkingen in de nierfunktie hebben zich niet voorgedaan. Wel is bij 4 patienten een tijdeljke stoornis van de leverfunkties aangetoond. Ondanks de goede resultaten bij deze kleine groep patienten bestaat twijfel over de juiste dosering van dit middel. De dalspiegels blijken laag. Gemiddeld is pas na 7 dagen behandeling de MIC 90 voor *Staphylococcus epidermidis* bereikt, hetgeen toch een van de meest frequent voorkomende, multiresistente, Gram-positief organisme is in deze patienten groep. De eerste resultaten van een

vervolg studie met hogere dosering laat echter mogelijk ook een toename van de bijwerkingen zien. Teicoplanin kan effectief zijn als additionele therapie bij neutropenische patienten met koorts die niet verbeteren op ceftazidime alleen, echter de juiste dosering moet nog vastgesteld worden.

hoofdstuk 6 Infecties met Gram-negatieve bacterien blijken, indien niet snel en adequaat behandeld, in een a twee dagen fataal te zijn voor het merendeel van de granulocytopenische patienten. Iedere behandeling van een infectie in deze patienten groep dient dan ook ten minste effectief te zijn tegen deze pathogenen. Het meest beruchte en moeilijkst te behandelen organisme is *Pseudomonas aeruginosa*. Analyse van alle granulocytopenische patienten die een sepsis met *Pseudomonas aeruginosa* doorgemaakt hebben en in eerste instantie met ceftazidime alleen zijn behandeld, wordt in dit hoofdstuk besproken. Alle patienten (29) zijn genezen, op een na die na 6 dagen behandeling is gestorven ten gevolge van een hersenbloeding. Wel is gebleken, dat in patienten met een plaatselijke onsteking de koorts en klachten langer aanhouden en de behandeling ook langer doorgezet is moeten worden, dan in patienten met sepsis zonder aanwijsbaar focus.

Hoofdstuk 7 Bekend is het probleen van nierfunktie stoornissen ten gevolge van cyclosporine-A, welke toegepast wordt bij allogene beennerg transplantatie om afstoting te voorkomen. De conventionele combinaties van antimicrobiele middelen neigen tot versterking van de nephrotoxiciteit van dit middel. In dit hoofdstuk beschrijven wij het onderzoek naar het effect van ceftazidime op de nierfunktie tijdens cyclosporine gebruik. De nierfunktie blijkt hierdoor niet verder aangetast te worden. De effectiviteit van ceftazidime alleen in deze groep patienten blijkt 72% te zijn. De genezing van bacteriologisch aangetoonde infecties is 63% bij een hoge incidentie van Gram-positieve microorganismen. Ceftazidime vormt een goed alternatief voor combinatie therapie na beenmerg transplantatie, ter voorkoming van nierfunktiestoornissen bij gelijktijdig gebruik van cyclosporine-A, indien men erop verdacht is de behandeling aan te passen zogauw zich een infectie met een resistent Gram-positief organisme voordoet.

Hoofdstuk 8 De behandeling van patienten met acute myeloide leukemie wordt gecompliceerd door een frequent voorkomen van door geneesmiddelen veroorzaakte huidreakties. Veel gebruikte middelen als allopurinol, co-

trimoxazole, miconazole en ketoconazole zijn bij remissie inductie en na recidief significant vaker geassocieerd met huidreakties dan in perioden van remissie. Bij 12% van deze patienten moet de behandeling aangepast worden tgv. een huidreaktie door penicilline derivaten hetgeen significant vaker is dan na het gebruik van cephalosporines (3%, p 0.001). Slechts eenmaal heeft zich een huiduitslag tgv. ceftazidime voorgedaan.

Hoofdstuk 9 Uit de literatuur blijkt dat infecties met een aantoonbaar focus minder goed reageren op behandeling dan infecties zonder duidelijke orgaan localisatie. Ter nadere evaluatie van de mogelijke rol van ceftazidime bij de behandeling van gelocaliseerde infecties zijn alle, tot 1986 met ceftazidime monotherapie behandelde patienten, opnieuw geanalyseerd. Bij 44% van hen wordt een focus aangetoond. Schimmels blijken vaker voor te komen bij infecties in de luchtwegen. Gram-negatieve pathogenen worden vaker geisoleerd bij een infectie van de urineuegen of bronchopneumonie. Gram-positieve microorganismen blijken vaker verantwoordelijk voor een sepsis zonder focus en voor een weke delen infectie. Alleen in dit laatste geval is modificatie van ceftazidime monotherapie significant vaker noodzakelijk dan in de overige gelocaliseerde infecties. Tenslotte blijkt dat, indien zich een gelocaliseerde infectie voordoet, de koortsperiode en klachten langer aanhouden en behandeling langduriger voortgezet moet worden dan bij infecties zonder aanwijsbaar focus. Mogelijk zal combinatie therapie in deze gevallen zinvol kunnen zijn, het bewijs hiervoor is echter nog niet geleverd.

Tot voor kort zijn infecties de belangrijkste doodsoorzaak geweest voor patienten met een hematologische aandoening gecompliceerd door granulocytopenie al dan niet na chemotherapie. Er bestaan aanwijzingen dat de mortaliteit tgv infecties afneemt gedurende de laatste 7 jaar in deze kliniek. Factoren die hierop van invloed kunnen zijn geweest zijn de introduktie van selectieve darmdecontaminatie, de vroegtijdige behandeling van de granulocytopenische patient met koorts, de ervaring die opgedaan is tijdens onderzoek en de introduktie van meer potente anti-microbiele middelen zoals ceftazidime.

Uit de verschillende studies blijkt dat ceftazidime monotherapie niet onderdoet voor conventionele combinatie therapie, met als voornaamste voordeel een lage toxiciteit gepaard gaande aan eenvoud van toediening.

Patienten met koorts zonder aanwijsbaar focus, of met weke delen aandoening dan wel na beenmerg transplantatie lopen een verhoogd risiko op infecties door Gram-positieve microorganismen. Ceftazidime is minder werkzaam tegen deze organismen, echter een stapsgewijze uitbreiding van de behandeling lijkt een veilig alternatief voor een initiele breedspectrum combinatie therapie. Deze opstelling kan de patient mogelijke bijwerkingen besparen en beperkt de totale kosten van behandeling. De hoge kosten van ceftazidime zelf vormen een nadeel. Echter, de extra kosten van combinatie therapie in de vorm van een toename van: arbeid, infuussystemen, spiegel bepalingen, kans op toxiciteit en daardoor noodzakelijke monitoring van funkties en of beschermende maatregelen, dienen mede berekend te worden naast de koster van de middelen zelf in de uiteindelijke keuze van de behandeling.

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Stans Verhagen, zoon van Con Verhagen en Riet van Strien, werd geboren op 15 november 1952 te Balikpapan (Indonesie). Van 1965 tot 1970 bezocht hij het Boschveld College te Venraij, alwaar hij in 1970 het getuigschrift Hogere Burger School B behaalde. Aansluitend studeerde hij geneeskunde aan de Katholieke Universiteit van Nijmegen. In 1974 trad hij in het huwelijk met Mieke Derks en samen verichtten zij gedurende een half jaar veldonderzoek voor "Primary health care" in Djezza (Tunesie) in 1977 (Koninklijk Instituut voor de Tropen; Hoofd ter velde: Drs. P. Verstraaten). Na het artsexamen in 1978 bekwaamde hij zich verder in de chirurgie, verloskunde en gynaecologie in het Koningin Juliana ziekenhuis te Hengelo (O) (chirurgen: Dr. A.H. Berkhoudt, Drs. P.H.A.J. Delfgauw, Drs. B.A. van Driel en Drs. H. Reynders; gynaecologen: Drs. J. Kropveld en Dr. H.A. van Opstall) en volgde de Tropen cursus te Amsterdam in 1980. Aansluitend werkte hij 3 jaar samen met zijn echtgenote in St. Mary's Hospital te Lumias (Kenia), het laatste jaar als "Medical Officer in Charge". In deze periode zijn 2 van hun 3 zonen geboren. Na repatriering in 1983 startte hij in de Universiteits kliniek St. Radboud ziekenhuis te Nijmegen op de afdeling Algemene Inwendige Geneeskunde (hoofd: Prof. Dr. A. van 't Laar) met de opleiding tot internist.

STELLINGEN

1 Antibiotica vormen de belangrijkste antipyretica voor neutropenische patienten.
(Sickles et al · Arch. Intern Med. (1975) 135, 715-719.
Klastersky : Rev. Infect Dis (1983) 5, S21-S31)

2. Ceftazidime monotherapie is even effectief als traditionele combinaties van antibiotica bij de behandeling van neutropenische patienten met koorts
(Dit proefschrift)

3. Ceftazidime monotherapie als empirische behandeling van de neutropenische patient met koorts verdient de voorkeur bij gelijktijdig gebruik van potentieel nefro- of ototoxische middelen
(Dit proefschrift)

4. Bij het bepalen van een behandelingsstrategie van een neutropenische patient met koorts dient rekening gehouden te worden met de eventuele localisatie van de infectie.
(Dit proefschrift)

5. De kans op door geneesmiddelen geinduceerde huidreakties is verhoogd bij patienten met een gecompromiteerde immuniteit.
(Dit proefschrift)

6. De handdruk van een arts bergt een groter risiko in zich op overdracht van pathogene micro-organismen dan gebruik van het toilet.
(Semmelweis . Die Aetiologie, der Begriff und die Prophylaxis des Kindbettfiebers (1861).
Just : Infections in the immunocompromised host. Symp (nov. 86) Nijmegen)

7. De verschuiving van Gram-negatieve naar Gram-positieve verwekkers van infecties bij neutropenische patienten kan niet toegeschreven worden aan de toepassing van selectieve darm-decontaminatie alleen.
(Guiot 4th. Int. Symp Inf. Immunocomp. Host, Ronneby (1986), Abstr. 92)

8 Overleving vormt de belangrijkste parameter voor de effectiviteit van een antibioticum bij een neutropenische patient met bewezen infectie.
(Pizzo . N. Eng J. Med. (1986) 315; 552-558)

9. Het voorschrijven van buscopan suppositoria bij darmkrampen of kolieken is alleen al op grond van farmacologische gegevens irrationeel te noemen.
(Martindale, The Extra Pharmacopoeia, (1982) 28th Ed London)

10 Hoewel de converting enzyme remmers vooral zijn ontworpen voor de behandeling van patienten met renovasculaire hypertensie lijken ze juist bij deze patienten in toenemende mate gecontraindiceerd
(Hoefnagels . Neth. J. Med (1984) 27, 269-274)

11. De superioriteit van de nieuwe polychemotherapie kuren zoals PROMACE-MOPP en M-BACOD bij maligne lymfomen over de meer traditionele combinaties zoals CHOP en MOPP is niet bewezen.
(Laurence . Ann. Intern Med (1982) 97, 190-195
Fisher Ann. Intern. Med (1983) 98, 304-309
Shipp Ann. Intern Med (1986) 104; 757-765)

12. Interferon alpha heeft de voorkeur boven splenectomie bij de behandeling van Hairy cell leukemie
(Porzsolt . Blut (1986) 52, 265-272)

13. Toename van de effectiviteit van orale rehydratie vloeistof door ontwikkeling van meer verfijnde commerciéle preparaten gaat ten koste van de bereikbaarheid.
Thuis bereidde oplossingen op basis van zout met suiker of rijst verdienen dan ook de voorkeur.
(Werner (1979) . Where there is no doctor
Molla The Lancet (1982) I; 1317-1319)

14. Om medische redenen verdienen gebieden met een minder intense malaria transmissie prioriteit te worden gegeven in de bestrijding van deze ziekte
(WHO Expert Committee on Malaria 18th report, Geneva 1986
Phillips : Quaterly J. Med. (1986) 227, 305-328)

15 Dat de subfaculteit der geneeskunde te Nijmegen "Hersenen en Gedrag" als zwaartepunt heeft gekozen, geeft te denken.

16. Bij ongebreideld bevolkingsonderzoek wordt voorkomen duurder dan genezen.

Nijmegen, 22 januari 1987 Verhagen C.A H.H V.M.