ANTIMICROBIAL AGENTS

PERILS AND PROMISE

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INFECTIOUS DISEASES SECTION

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Case Report #1. W.M. is a 70 year old white male who has been paraplegic for 18 years following a gun shot wound. He has had a chronic indwelling urinary catheter for 14 years with recurrent admissions for fever and cloudy urine. He was admitted in June with a one-week history of cloudy urine, oliguria and fever. He had a past history of peptic ulcer disease but he had no recent bleeding, aspirin ingestion or alcohol use. His appetite had been good prior to the onset of illness. Physical examination showed a well nourished white male with a temperature of 37.7°C. Abdominal examination revealed a palpable bladder. He had a posterior scrotal urethreostomy with purulent urine in the drainage tubing. Stool was guaiac negative. Neurologic exam revealed paraplegia with sensory deficit at T12 area.

Initial blood studies showed a hematocrit of 41 with normal indicies, platelet count 290,000/mm^3, WBC of 14,400/mm^3 with differential of 76 neutrophils, 4 bands, 12 lymphocytes and 8 monocytes. Prothrombin time was 11 seconds. Serum chemical analysis were unremarkable except for creatinine of 3.3 mg/dl and BUN of 26 mg/dl. UA showed a pH of 7.1, negative protein and 20-25 WBC (hpf), 1-3 RBC/hpf and many bacteria on microscopic examination.

Initially gentamicin was begun for presumed urinary tract infection and later penicillin and trimethoprim/sulfamethazole were added. The patient's urine culture grew Pseudomonas aeruginosa and Proteus mirabilis sensitive to amikacin and cefoperazone. Blood cultures were sterile. Sonogram revealed mild hydronephrosis on the right. His temperature spiked on the hospital day to 102.3°. When the results of susceptibility testing were reported, he was switched to amikacin and promptly became afebrile. Serum creatinine progressively rose to 7.7 mg/dl. In addition, he was noted to have a decreased urine output. Consequently he switched on June 9 to Cefaperazone 2 grams q 12 hours. On this day his hematocrit was 31, having responded to volume replacement. His prothrombin time was 12.1 seconds (11 seconds control and partial thromboplastim time was 24 seconds (control 25.2 seconds). Platelets were 206,000 per mm^3. Five days later he was noted to have gross hematuria in the urine bag and a nasogastric aspirate showed coffee ground material with positive guaiac. The following day he had bright red blood in his stool and the nasal gastric aspirate. The hematocrit had fallen at this time was 24. Repeat coagulation studies showed the prothrombin time to be 35.8 seconds (11.1 seconds control) and PTT was 39.5 seconds (24 seconds control). Platelet count was 366,000 mm^3.

He was treated with antacids and cimetidine and was transfused with 2 units of packed red cells. Cefoperazone was discontinued, Vitamin K 10 milligrams was given subcutaneously for three days, and two units of fresh frozen plasma were also given. His clotting studies returned to normal within 24 hours. He was transfused with three more units of packed red cells with stabilization of hematocrit at 31. A repeat urine culture was sterile. A CT scan showed a right perinephric clot and bladder clot with ureteral blockage on the right side. Consequently a percutaneous nephrostomy was performed for urinary drainage. Since he had persistence of the perinephric clot, exploratory surgery was performed to remove a large retroperitoneal collection of blood. Microbial culture was negative. He was remained hospitalized for the next three months with repeated ureteral tube insertions and multiple surgical drainage procedures. Presently he has a large flank wound closing by secondary intention.

That a bleeding diathesis can be associated with administration of β - lactam antibiotics has been known for some two decades. (1,2) Although bleeding can occur with any of the β lactam antibiotics, it has been recognized recently to be particularly associated with the use of newly introduced cephalosporin; cefamandole and moxalactam. (3,4) Impairment of hemostasis by β - lactam antibiotics can result from one or a combination of three mechanisms: (1) Indirect inhibition of fibrin formation through inhibition of synthesis of vitamin K - dependent coagulation factors; (2) inhibition of normal platelet function, and (3) direct inhibition of fibrin formation through inhibition of the final phases of blood coagulation. (3) A bleeding problem due to low levels of clotting factors that depend on vitamin K for their biosynthesis (clotting factors II, VII, IX and X) has a predilection for elderly patients who are debilitated and/or patients on hyperalimentation, but complications also have been noted in young healthy patients. (4-6) Presumably they weren't eating for some period prior to the treatment. Some have postulated that these antibiotics diminish the production of Vitamin K in the gastrointestinal tract in previously starved individuals (3). However, a duration of 3 to 4 weeks is necesary before hypoprothrombinemia follows the combination of starvation and antibiotic administration (7). Hence this is an unlikely explanation for the very rapid development of hypoprothrombinemia within 4 to 6 days of therapy with resultant bleeding difficulties as seen in our case. The bleeding diathesis is rapidly reversible with administration of Vitamin K and there is no associated defect in platelets or fibrinogen (5,6).

In experimental studies, cefamandole and moxalactam did not have a direct inhibitory effect on Vitamin K dependent clotting factors (3). Assays for Vitamin K and the clotting factors II, VII, IX and X and for the Vitamin K independent clotting factors V and VIII were normal. In addition there was no abnormal prothrombin precursor such as appears in patients taking warfarin. Thus no experimental evidence has been garnered to explain such a rapid change in prothrombin time. The one characteristic of the cephalosporins associated with these changes is the methylthiotetrazole side chain at position 3 (figure 1). No experimental published studies have been done to assess the effect of this metabolite on prothrombin synthesis.

This ring is also probably responsible for the antabuse-like reaction reported with these same antibiotics (table 1) in patients who drink alcohol after receiving the drug (more likely in hospitals with bars!). (8)

This disulfiram reaction with moxalactam is associated with accumulation of acetaldehyde, likely through inhibition of aldehyde dehydrogenase (8). Computergraphics indicated close match for the S-S-C-N-C chain in disulfiram with the C-S-C-N-C chain in the methythiotetrazole structure of moxalactam (figure 2).

Previous studies have shown that many β -lactams, most especially the carboxypenicillins induce platelet dysfunction (3). The defect results from the interaction of aggregation agonists with the appropriate platelet membrane receptors (9,10). Carbenicillin was shown to reduce aggregation of an adenosine diphosphate (ADP) affinity label to the binding protein in platelet membranes (10). Prolonged bleeding times (greater than 7 minutes) have been noted in patients receiving carbenicillin within 3 days (9). Bleeding diatheses however have

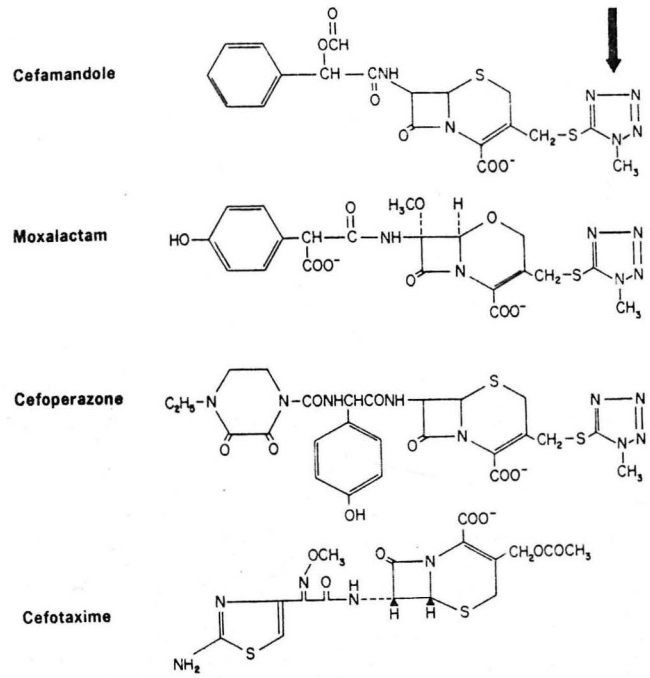
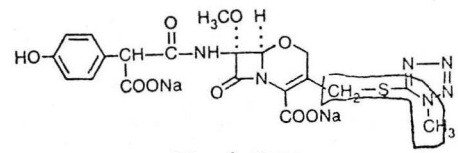


TABLE 1

DISULFIRAM-LIKE REACTIONS IN THOSE WHO INGEST ETHANOL WITH ANTIBIOTICS

METRONIDAZOLE
FURAZOLIDONE
CHLORAMPHENICOL
GRISEOFULVIN
SULFONAMIDES
CEFAMANDOLE
CEFOPERAZONE
MOXALACTAM



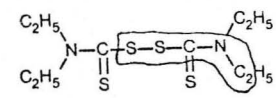


Figure 2: Structures of moxalactam and disulfiram.

generally occurred in those with renal failure, indicating the additive effects of bleeding abnormalities in renal failure with the adverse effects of these penicillins on perturbation of the platelet membranes. A great majority of lactam antibiotics suppress platelet aggregation when tested in vitro but in concentrations far greater than in those achieved in vivo (3). Moxalactam was shown to affect platelet function in vivo in normal subjects given standard dosing. The defect reached a maximum at six days and the ADP aggregation abnormality returned to normal within 96 hours after the last dose. Bleeding diatheses have been reported to result from prolongation of the bleeding time with impaired ADP aggregation of platelets (11). These authors postulate the defect may be additive with other factors that affect platelet function: azotemia, heparin, antihistamine, aspirin and other antiinflammatory agents, furosemide, propranolol and steroids (11).

Practical considerations

Since the cephalosporins (cefamandole, cefoperazone, moxalactam) which lead to bleeding problems secondary to hypoprothrombinemia develop the abnormality within 4 to 6 days after administration of the antibiotic, it is wise to premedicate with 10 mg Vitamin K prior to giving these drugs. Even with this therapy, 20% of granulocytopenic patients receiving moxalactam had an elevated prothrombin time with therapy, requiring further administration of Vitamin K (12); hence a repeat study is required at 4-5 days. Recently, the package insert for moxalactam was changed to recommend preventive treatment with Vitamin K of debilitated elderly persons receiving moxalactam. Case reports indicate it occurs also in young people, so I suggest all receive Vitamin K and have protimes checked. I also recommend this be done for patients treated with cefoperazone and cefamandole (5,13). All patients on β-lactams with any drug having an effect on platelet function or with a disease with platelet abnormalities (renal failure, leukemia) should be observed closely for bleeding abnormalities. Dosing of drugs should be checked since it is with extremely high levels of β lactam antibiotics that bleeding diatheses occur, especially in patients with renal failure. Blood levels can be obtained within 6 hours by Dr. Bawdon. Administration of fresh frozen plasma with vitamin K may be required in patients with extensive bleeding as in our case.

NEW β LACTAM ANTIBIOTICS

A number of new β lactam penicillins have been introduced to provide an impressive number of new penicillins. The amino, carboxy and acyl-ureido penicillins provide a much wider spectrum against gram negative bacilli than do the benzyl penicillin derivatives. The acyl-ureidopenicillins include azlocillin, mezlocillin, and piperacillin. These are generally more effective against klebsiella and other gram-negative rods than the carboxy-penicillins. In general, azlocillin is more potent than mezlocillin against Pseudomonas but less active against Enterbacteriaceae. These strains are bactericidal for the organisms resistant to carboxy-penicillins but they are susceptible to inactivation by chromosomal β lactamase of the organism, especially at large inocula in vitro (14). Hence, it is unlikely that these antipseudomonal penicillins will be adequate as single agents for treatment of severe pseudomonas infections. Pipraicillin also has broader spectrum activity than carboxypenicillins against gram negative bacilli (15). Although an occasional study has

TABLE 2

THE "NEW" β LACTAM ANTIBIOTICS (22)

Chemical/Generic	Feature	Disadvantages: Microbiologic	Disadvantages: Pharmacologic	Recommended Use
Aminopenicillins Amoxicillin	Active for: E. coli, H. Influenzae Salmonella	Susceptible to β Lactamase	GI, skin rash (10%)	UTI, URI, (Bacterial) salmonella, Meningitis (neg β Lactamase)
Carboxycillins Carbenicillin Ticarcillin	Active against pseudomonas (80%) Enterobacter, Indole + Proteus	Resistance develops on Rx, with use alone	HypoKalemia (equivalent) Platelet defect	1st infection immuno-compromised (with aminoglycocides)
Acyl-ureido penicillins Azlocillin Mezlocilin Piperacillin	Active against Pseudomonas (90%) Enterobacter Klebsiella	Resistance develops on Rx Less effective with higher inocula	HypoKalemia, neutropenia, skin rash	Infections in immuno-compromised patients, with aminoglycosides
Miscellaneous Lactamase Inhibitor Clavulanic acid amdinocillin	Extending spectum for amino penicillins, cephalosporins	Has to be combined Increased efficacy questionable	Coombs test positive otherwise same	Uncertain
Monobactam Aztreonam	Gram negative including pseudomonas (60%)	No activity for gram pos. or anaerobes	Allergic, Liver function	Urinary tract recurrences pneumonia with resistant organisms
Thienamycin Imipenem	Gram negative including pseudomonas (98%) B. fragilis: resistant to β Lactamase	Few	Must be combined with inhibitor of renal peptidase	Uncertain but may be effective single agent for abdominal infections

been done using piperacillin as a single agent (vancomycin was added to provide more adequate gram positive coverage for staphylococcus) most studies have evaluated the combination of piperacillin with aminoglycosides or occasionally with a cephalosporin with antipseudomonal activity (16-17). Piperacillin was either only slightly more effective or was equally effective as the carboxypenicillins combined with aminoglycosides in treatment of the granulocytopenic patient. Superinfection with resistant organisms has been noted more frequently with piperacillin than with azlocillin (17). The frequency of hypokalemia is low with azlocillin and mezlocillin but occurs in up to 20 percent in trials with piperacillin; in fact, the frequency is equivalent to that seen with either ticarcillin or carbenicillin (16). Hypersensitivity reactions, including skin rash, can occur with any of these agents but in one study was shown to be increased with azlocillin (18). Neutropenia, the most frequent hematologic manifestation with these new penicillins, was frequently noted (27%) in children given piperacillin (19). These agents also alter platelet function but less so than carbenicillin (20). In addition up to 30% of mezlocillin may be excreted via the biliary route so dosing must be tailored to liver function studies (21). These drugs are relatively safe agents for use in serious infections, particularly immunocompromised and/or granulocytopenic patients, but combination with aminoglycosides is recommended. Such combination will provide either additive or synergistic bactericidal effect and could delay the emergence of resistance to one or more of the components of the combination (14).

Other miscellaneous β lactam antibiotics are being introduced which either can be combined with penicillins to make them more active or are distant relatives with broad activities. Clavulanic acid has low antimicrobial activity per se, but will inhibit β -lactamase, particularly those common in gram negative bacilli (22). Clavulanic acid and amdinocillin consequently are formulated with amino and carboxypenicillins to extend the bacterial spectrum of these penicillins since these agents are highly susceptible to β-lactamase (23). Although the use of such combination for upper respiratory tract infections including sinusitis and otitis media, urinary tract infections and even for scattered reports of severe systemic bacterial infections show efficacy, it has been difficult thus far to determine that the combination is more effective than the parent drug (23,24). These compounds then have great theoretical attraction, but limited objective evidence for augmenting clinical efficacy is exact. Recently in vitro activity of a combination of clavulanic acid against M. tuberculosis (which produces a β-lactamase) was shown (25). Very little added side effects have been noted with the combination except for a slightly increased frequency of positive Coomb's test, without evidence of hemolysis. The role of the combination in adult infection is highly suspect, but the combination may have use in pediatric practice, especially if β lactamase containing strains continue to increase in frequency (26).

The monobactam antibiotics have been introduced with great "hoopla" as an entirely new class of antibiotic. Aztreonam, the monobactam with greatest clinical experience has been effective against a great proportion of gram negative bacilli, including pseudomonas, and has been shown clinically efficacious for susceptible organisms (27). The compound has no activity for gram positive organisms or anaerobes so that combination therapy must be resorted to prior to bacterial identification for most non-UTI infections. The principle use of this agent might be in recurrent urinary tract infections, since the drug appears to

be highly effective, even in upper tract infections in men (Mackowiak). It also may have a role in treating pneumonia due to gram-negative resistant organisms; however, it is not known if resistance will develop to this antibiotic since it has only been used in limited clinical trials. Side effects are similar to those of the penicillin derivatives, including allergic rections and mild to moderate liver function abnormalities; however, there appears to be limited cross reactivity with the penicillin derivatives (28). Pending further studies, its use in penicillin-allergic patients should be cautioned. Finally, thienamycin, a carbapenem, will soon be released for clinical use. N-formimidoyl thienarycin (imipemide) has a very broad spectrum activity against gram positive, gram negative (including pseudomonas), and anaerobes, including Bacteroides fragilis (29). The antibiotic is resistant to β lactamase. Clinical trials have shown successful therapy alone with this agent although a dipeptidase inhibitor must be included with the antibiotic to prevent breakdown of the antibiotic in the kidney. Although renal toxicity was an early feature, this is apparently no longer noted with presently marketed drugs. The drug may have clinical use, particularly as a single agent for abdominal infections, although an occasional failure has been noted in severe complicated infections with bowel perforation (30).

The introduction of new cephalosporins has led to an unprecedented array of clinically effective drugs whose place in modern chemotherapy remains to be established. For the clinician, these agents offer promise of more clinically effective β lactams without the toxicities of the aminoglycosides (31). As the first case presented today indicates, clinically significant side effects have been detected with these agents; hence the molecular changes result in new pharmacologic properties as well as microbiologic effectiveness. The new groups of compounds offer sequentially more activity against aerobic gram negative rods and the most recently introduced agents offer varying activity against pseudomonas; in some cases, activity against anaerobic organisms is also demonstrated (Table 3). Whether these drugs can be used as single agents in therapy of infections due to these micro organisms remains uncertain, in spite of their effectiveness against pathogens tested at DVAMC (Table 4), Cepalosporins are indicated as drugs of first choice only for treatment of enteric gram negative bacillary meningitis and infections likely to be due to Klebsiella pneumoniae, such as gram negative bacillary pneumonia. In spite of in vitro susceptibility for Enterobacter, Serratia and Pseudomonas sp., these antibiotics are not just drugs of choice but alternative agents requiring careful clinical monitoring. In the granulocypenic, they probably should be combined with an aminoglycoside. One report indicated that cefotaxime + amino glycoside was less effective than azlocillin plus AG (32). For abdominal infections, these drugs may offer a single drug approach (as long as enterococcus is not an offending organism), although cost and efficacy may be equivalent with combinations of clindamycin with an aminoglycoside. Although each of the new parenteral cephalosporins are effective in urinary tract infections, close follow-up of these patients is required. Clinical trials of urinary tract infections in either single dose or prolonged therapy showed lower efficacy for oral cephalosporins than for trimethoprim/sulfamethaxazole or with ampicillin or amoxicillin (33-35)(Table 5). Recently, Cefamandole was shown to be less effective for men with UTI than Azreanam, (P. Mackowiak). Gram negative meningitis due to Enterobacteriaceae can be successfully treated with cefotaxime or moxolactam with greater success rates (80-90% success) than with earlier used anti-

TABLE 3

The Cephalosporins: based upon the following features: chemical structure, antibacterial activity, beta-lactamase stability and metabolic stability.(22)

	MICs (mg/l) of cephalosporins for 5 groups of organisms (% susceptible at DVAMC or PMH)			
	Gram +	Entero-bacteria + Haemophilic*	Pseudomonas	Bacteroides
Group I: Oral group. The antibacterial activity of these compounds is relatively low compared to parenteral cephalosporins. They are stable to Gram-positive beta-lactamases and to some Gram-negative beta-lactamases.				
Cephradine)	1 - 4	4 - 8	128	128
Cefaclor)	1 - 4	1	128	128
Cephalexin)				
Group II: Gram-positive group. Orginally introduced because of their high activity against penicillinase-producing staphylococci. The activity against Gram-negative rods is relatively low. Group IIa are metabolically stable but Gro= IIb are desacetylated with diminution of antibacterial activity.				
a) Cefazolin	0.03	1 - 2	128	32 - 64
b) Cephalothin; Cephacetrile		(40-60)		

*includes Haemophilus, Bordetella, Legionella, Campylobacter

	Gram +	Entero-bacteria + Haemophilic*	Pseudomonas	Bacteriodes
Group III: Gram-negative group. Compounds with high activity against many aerobic Gram-negative rods and stability to many beta-lactamases produced by these bacteria. Group IIIb is metabolically unstable (see IIb). Highest activity against Haemophilus influenzae is seen in this group.				
a) Cefamandole; Cefuroxime)	0.5 - 2	0.06 - 1 (80%) (95%)	32 - 128 (0) (20)	8 - 64
b) Cefotaxime)				
Group IV: Pseudomonas group. Compounds which exhibit high activity against Pseudomonas strains in addition to activity against Entero-bacteria. Group IVa are more stable to plasmid-mediated beta-lactamases.				
a) Ceftazidime	4 - 32	0.25 - 0.5 (95)	1 - 2 (90)	16
Ceftriaxone	4 - 32	0.25 - 1 (95)	4 - 8 (50)	2 - 32
b) Cefoperazone	1 - 8	0.25 - 2 (80)	4 - 8 (80)	4 - 8
Cefsulodin	2 - 8	128	2 - 4 (90)	128
Group V: Cephamycins. Anaerobe group. Compounds with 7- - methoxy group conferring high stability to beta-lactamases of aerobic and anaerobic bacteria.				
Cefoxitin	2	2 - 4 (80)	128	4 - 8
Moxalactam	4 - 16	0.25 - 0.5 (90)	8 - 16 (50)	0.5
Cefotetan	-	0.06	128	4 - 32

TABLE 4

ANTIMICROBIAL SUSCEPTIBILITY TESTING
DVAMC SEPT. 83

	Blood Isolates of Gram Negative Bacilli (%)
AMIKACIN	92
MOXALACTAM	89
CEFOTAXIME	86
GENT/TOBRA	81
CEFOPERAZONE	78
TMP/SMX	76
PIPERACILLIN	73
CEFOXITIN	70
CEFAMANDOLE	57
CARBENICILLIN	51
CEPHALOTHIN	41
CHLORAMPHENICOL	30
TETRACYCLINE	30
AMPICILLIN	16

TABLE 5

SUCCESSFUL TREATMENT OF URINARY TRACT INFECTIONS (33-35)

Women	Dosage	Response(%)
TMP/SMX	160/800	94-100
Amoxicillin	3g	100
Netelmicin	150mg	95
Doxycycline	300mg	82
Cefuroxime	1.5g	79
Piv mecillinam	600mg	77
Cefaclor	2g	43
Cephaloridine	2g	35

TABLE 6

Summary of past and present efficacy data for treatment of experimental Pseudomonas pneumonia. (38)

Drug	Survival (%)
Tobramycin	79
Thienamycin	75
Moxalactam	47
Cefoperazone	39
Cefsulodin	39
Ceftazidime	38
Ticarcillin	35

biotics including ampicillin or chloramphenicol (36). These agents are effective bvecause they achieve CSF levels tenfold above MBC (37). However, ampicillin may need to be added to these agents until it is proven that the infection is not due to Listeria (the most common agent in the immunocompromised patient with meningitis). Penicillin must be included in any patient given moxolactam since neither the pneumococcus nor group B strep respond to this agent. Treatment of pseudomonas meningitis is best done with the combination of an aminoglycoside given intravenously and intrathecally, combined with anti-pseudomonus penicillin such as carboxypenicillin or piperacillin (36). All of the newly introduced cephalosporins have been evaluated as prophylactic agents for surgery. There is no evidence that these new cephalosporins offer any advantage over the less expensive cephalosporins particularly cefazolin. I am comfortable with the policy in force at the DVAMC in which a single parenteral cephalosporin, as cephapirin, is available for treatment of infection in the organisms susceptible to cephalothin and as an alternative for serious infections in a penicillin allergic patient (with very careful monitoring of patient since 10% of patients manifest cross reactivity). Expensive oral cephalosporins requires approval for patients who cannot tolerate less expensive agents such as semisynthetic antistaphylococcal drugs or erythromycin. Indications for parenteral cephalosporins include spontaneous bacterial peritonitis in the patient with ascites (cefamandole or moxalactam), and gram negative bacillary pneumonia (cefamandole), but toxicity (hypoprothrombinemia) has to be monitored carefully. New cephalosporins were less effective than aminoglycosides and thienamycin for experimental pneumonia (38) (Table 6). They also are not as effective for B. fragilis as with other agents (39)(Table 7). Otherwise, antimicrobial susceptibility testing that indicates that a parenteral cephalosporin is effective, especially in a patient with renal failure, would be reason to substitute a cephalosporin for an aminoglycoside. Granulocytopenic patients with potential for pseudomous infection (Table 8) would best be treated either with a carboxypenicillin or acylpenicillin with an aminoglysocide (40).

Infections in granulocytopenic patients: Facts vs Myths

These patients are predisposed to such infections due to host factors and other human factors. There is an inverse relationship between the number of circulating leukocytes in the frequency of infection with an increase of frequency from 4% when the wbc exceeded 1,000/mm^3 to 43% per 1,000 days when the count was less than 100/mm^3 (Table 9)(41). Recent studies indicate that the inanimate environmental reservoirs such as air, sink drains and water are unlikely to be the primary source of organisms responsible for nosocomial infections (42). Since certain uncooked foods, particularly salads and nonprocessed dairy products containing specific pathogens, it is reasonable to decrease the risk of such acquisition in granulocytopenic patients by using a cooked food diet and the avoidance of salads, especially tomatoes (43). There is no justification for the previous common practice of placing patients in protective isolation (single room, gowns, masks, and gloves) nor is there any evidence that this reduces colonization or frequency of infection. A program which emphasizes handwashing by medical nursing personnel is presently recommended. Studies show that fewer than 30% of physicians caring for seriously ill patients in intensive care unit consistently wash their hands (44). Reemphasis of handwashing to prevent transmission of potential pathogens is to be emphasized.

TABLE 7

Susceptibility of agents effective for Bacteroides fragilis (39)

	% Susceptible	Breakpoint
Metronidazole	100	8
Chloramphernicol	100	8
Clindamycin	94	4
Cefoxitin	92	16
Piperacillin	88	64
Moxalactam	78	16
Cefotaxime	46	16
Cefoperazone	43	16
Tetracycline	37	4

TABLE 8

Susceptibility of Pseudomonas aeruginosa to Newer Beta-Lactam Antimicrobial Agents (40)

Agent	No. Tested[1]	MIC Range (μg/ml)	MIC_{50} (μg/ml)	MIC_{90} (μg/ml)	Per Cent Susceptible[2]
Azlocillin	525	1- 512	32	128	92
Aztreonam	621	1- 64	4	64	60
Cefoperazone	985	1- 64	8	64	89
Cefotaxime	771	1- 64	32	64	58
Cefsulodin	426	1- 128	4	32	93
Ceftazidime	305	2- 64	8	64	88
Mezlocillin	420	2- 512	64	256	80
Moxalactam	1320	2- 128	32	64	51
Piperacillin	746	1- 512	16	256	87
N-formimidoyl-thienamycin	478	0.5 64	2	8	98

[1]Total number of isolates tested = 1422. All isolates not tested against each agent.

[2]Susceptible to clinically relevant serum levels.

TABLE 9

NEUTROPENIA AND SEVERE INFECTION (BODEY)

Neutrophil Count	Days at Risk	Episodes of infection per 1000 days
2000	6409	3.8
1501-2000	2231	3.9
1001-1500	2725	3.7
501-1000	2034	10.5
101- 500	1663	19
100	772	43

TABLE 10

Response of febrile neutropenic patients to combination antibiotic therapy (45)
(Ticarcillin + Moxalactam vs. Ticarcillin + Tobramycin)

	% Response
Microbiologically documented	47
Bacteremia	45
Pneumonia	67
Wbc >100 during therapy	71
Wbc <100 on therapy	31

TABLE 11

Clinical results of antimicrobial combination with or without synergy (46)

		Without	With
GNB Bacteremia	Pen + AG	49	80
GNB Bacteremia	Cbn + Amik	41	75
GNB Bacteremia	β lactam + AG	33	79
GNB Bacteremia	Cbn +AG	43	82

TABLE 12

Response rate (%) with various combinations in granulocytopenic patients (32)

	Axlo + Amik	Cefotaxime + Amikacin	Ticarcillin + Amikacin
Bacteremia	60	31	48
GNB Bacteremia	56	30	33
Proven Infection	76	72	64
All infections	69	63	56

Infections in granulocytopenic patients: efficacy of antimicrobial agents.

A number of antibiotic trials of emperic therapy in febrile granulocytopenic cancer patients show that the response relates to improvement in leukocyte count (Table 10) and correlates with achieving a bactericidal activity of serum exceeding 1:8 (Table 11) (45,46). Unfortunately many recent studies do not document the bactericidal activity of the regimens studies, thus hampering evaluation of new antibiotics in therapy. Most anti-microbial susceptibilities are given as minimum inhibitory concentrations (MICs) rather than minimum bactericidal concentrations (MBCs), so it is difficult to make assumptions concerning cidal activity. With the availability to multiple cell wall active drugs which bind to different penicillin binding proteins (PBB), the possibility of obtaining synergisms with two β lactam agents has been attempted. Although multiple studies show that single agents may be moderately effective in clinical infections in cancer patients, most therapeutic trials in the granulocytopenic patient have been with combinations of antibiotics. In some studies combinations of mezlocillin or moxalactam with either ticarcillin or piperacillin have shown either equal or reduced activity against gram negative infections (12, 45, 47). In another study, cefotaxime and ticarcillin combined with amikacin were less successful than azlocillin combined with this aminoglycoside for neutropenic patients with bacteremia (32). The failures in ticarcillin group related to insufficient antimicrobial activity whereas cefotaxime related to therapeutic failures with susceptible organisms. However when all infections are included with microbiologic data, there was no significant difference in any of the three combinations (Table 12). Thus large groups of patients are required to indicate if differences occur with a therapy given regimen for severe infections in granulocytopenic patients. Another factor that needs to be considered when aminoglycosides are included in the combination is potential difference that occurs with different aminoglycosides. In vitro studies indicate greater synergy with combinations containing amikacin followed by netelmicin and gentamicin (48). The lowest rate of synergy is seen with combinations containing tobramycin. Unfortunately inadequate data is available in many of these studies to determine if bactericidal activity is present and might account for differences in response rates in bacteremic patients.

A justification for combinations of two β -lactam antibiotics would be to diminish the frequency of side effects. Most studies of combinations including aminoglycosides indicate rates of nephrotoxicity in the 3% to 5% range in granulocytopenic patients (12,45). Hypersensitivity reactions may be more frequent (14%) when two β -lactam drugs were used and a significant increase in prothrombin time was noted in 20% or more of patients given moxolactam, even in those pretreated with 10 mg of Vitamin K, (12,45). Hypokalemia also occurred in approximately 20% of patients receiving β -lactam antibiotics whether the antibiotics were ticarcillin or piperacillin (16,17). Hence, combination therapy with drugs likely to lead to synergy is recommended: the best choice requires further study, but carboxy penicillins and aminoglycosides (amikacin and gentamicin) appear to offer best efficacy (46,49).

Persistence of Gram Negative Infection Due to Inducible β Lactamase: Species Specific but not antibiotic specific

One hazard of administering single β lactam antibiotics to granulocytopenic patients or any patient with serious infection is the development of

resistance during therapy (50). This rarely happens when combinations are used. Such events relate to the presence in gram negative bacilli of chromosomally mediated cephalosporinases which can be induced by the newer cephalosporins. These enzymes are species specific and are present in Enterobacter, Serratia and Pseudomonas sp.(51). These enzymes attracted little attention since the initially introduced cephalosporins were inactive against strains possessing them; however, these enzymes have attained clinical importance recently. The persistence of infections due to organisms which apparently alter resistance pattern results from induction or derepression of the β lactamase, either through mutation to a derepressed state or reversible derepression of the wild type by an enzyme inducer (51). Once these β lactamases are derepressed or induced, the strain becomes resistant not only to the β lactam antibiotic being used in therapy but to multiple β lactam antibiotics, including many of the new compounds not hydrolyzed by the enzymes. In the derepressed state there is an increase in β lactamase molecules in the periplasmic space, so that the substrate antibiotic appears to be bound and then hydrolyzed to the inactive form before it can gain access to the target proteins. (Figure 3)(51). Most β-lactam antibiotics including the antipseudomonal penicillins, recently developed cephalosporins may be affected by these enzymes. (Table 13 - case of Dr. Ed Goodman's). So far the only β lactams unaffected are those that bind primarily to penicillin binding protein 2 in gram-negative bacilli: mecillinam. This inducement of β lactamase leading to multiple β lactam resistance has been shown to be responsible for the emergence of resistance during therapy with cefamandole, ceftriaxome and moxalactam. The patients at risk are those with serious infection, usually with bacteremia with an organism possessing an inducible β lactamase. The resistance to these cephalosorins is not detectible by the susceptibility test routinely performed in hospital laboratories (either as Kirby-Bauer test or new rapid procedures). To detect this resistance, greater than 10^5 colony forming units (CFU) per ml have to be used; this is not routinely done in susceptibility testing but could be done with a tube dilution system. Close observation should be done on any patient given cephalosporins for enterobacter infections; if the patient fails to respond to the antibiotic, repeat cultures should be done and if the organism is reisolated, then susceptibility testing will show the organism to be resistant to the antibiotic used. This induction has been frequently noted with cefoxitin in the therapy of serratia infections, but has also been noted with enterobacter with cefamandole and moxalactam (50,51). Presumably, addition of aminoglycosides would prevent the appearance of these inducible organisms.

Aminoglycoside Dosage Prediction

Prediction of appropriate dosing of aminoglycosides has been attempted with nomograms. Variable dosage and variable frequency regimens have been compared (52). Recently, a computer-assisted aminoglycoside therapy plan has been used by clinical pharmacologists at DVAMC and PMH (M.E. Burton, D.C. Brater, and M.R. Vasko). They tested whether predictive dosing algorithm program incorporating Bayesian feedback program could more accurately predict drug dosages to achieve therapeutic serum levels than could individual physician judgement. Three groups were compared: control who had dosage determined by housestaff, a predictive group who had computer predicted dosage without serum level, and Bayesian group who had dosage altered after levels were obtained. Measurements of precision (bias and root mean squared prediction error) and correlation coef-

TABLE 13

DEVELOPMENT OF RESISTANCE TO β-LACTAM ON THERAPY (GOODMAN)
PSEUDOMONAS OSTEOMYELITIS ON CEFOPERAZONE

	BEFORE (MIC)	1 MO LATER (MIC)
MOXALACTAM	64	> 64
CEFOPERAZONE	16	128
PIPERACILLIN	16	64
MEZLOCILLIN	64	128
CARBENICILLIN	64	64

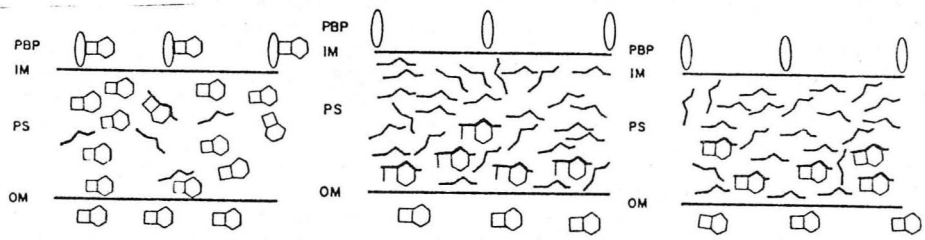


FIGURE 3. Development of resistance to multiple β-lactam antibiotics in gram-negative bacteria possessing inducible β-lactamases. In the uninduced state (left), there are very few β-lactamase molecules (~) in the periplasmic space (PS), and β-lactam antibiotics (⊂) freely pass through and attach to their target penicillin-binding proteins (PBP). Following derepression, there are many more β-lactamase molecules in the periplasmic space. These either bind and hydrolyze substrate drugs (middle) or prevent access by nonsubstrate drugs (right) to their target PBPs via a nonhydrolytic barrier. OM = outer membrane; IM = inner membrane.

ficient were made. Analysis of the bias for under predicting peak concentrations showed the housestaff predictions were low by 2.2 mg/dl, nomogram by 1.3 and Bayesian was 0.1. Predictions of trough were over predicted by housestaff at 0.7, predicting method 0.0 and Bayesian by 0.2. The correlation coefficient for house staff was 0.69, predicting method 0.83 and Bayesian 0.90 with the latter having a slope of unity. Hence the Bayesian method was more precise than either predicting method or housestaff intuition in determining and varying the dose needed to achieve target peak and trough serum concentrations of aminoglycosides. Programs are available at DVAMC and PMH for predicting and monitoring dosages of all aminoglycosides and vancomycin after serum levels are obtained. Values for serum concentrations can be obtained at DVAMC within 2 hours. Only one patient of 44 entered in the prospective trial developed a significant rise in creatinine on therapy. However nephrotoxicity and ototoxicity relate to multiple risk factors, including age, volume status, sex, liver disease but most importantly pre-existing renal disease (CF. Case #1) (53). Netilmicin and tobramycin are reputed to be less nephrotoxic than gentamicin, and netilmicin to be less ototoxic but the frequency of these side effects varies with the study (54). At least it is possible to follow patients carefully and alter dosage with precision, hopefully before nephrotoxicity or ototoxicity ensues!

Drug Fever

Many medications can result in fever which may prolong the patients hospital stay and result in extensive clinical evaluation before the drug is recognized as the cause of fever. Because of clinical problems seen at the Parkland and VA with drug fever, the subject was reviewed by Drs. Lemaistre and Mackowiak. Eighty-seven possible cases were reviewed of whom 43 patients were established to have had significant temperature elevation resulting from drug therapy. Fifty episodes of fever occurred in these 43 patients, of whom 29 episodes were due to an antimicrobial agent and 21 were due to other drugs. (Table 14) Although other series report increased risks for females, the patients were evenly distributed with 25 males (8 from the DVAMC) and 18 females. Elderly patients also are claimed to be at increased risks, but the age range was from 19 to 76 with a mean age of 45 and median of 50. The most commonly associated drugs are perhaps the most commonly used antimicrobial agents: penicillin, methicillin and cephalosporins. The interval from treatment to fever could be quite short: three days or less in four of nine cases with penicillin and all five cases with fever due to cephalosporin were within 48 hours of treatment. In four of these cases, the patients had had a previous history of drug fever: three occasions with penicillin derivatives and once with lincomycin. The duration to fever was quite short also for the sulfonamides, vancomycin, salicylates, IM ferrous dextran and with halothane. The latter case had developed fever previously, 11 days after halothane and died secondary to the liver failure following the second halothane exposure. The duration to fever was quite prolonged for cases with diphenylhydantoin with six cases occurring between thirty to sixty days after beginning therapy. However, fever developed within three days upon rechallenge with the drug in one case. The longest duration of therapy was with benztropine (cogentin) who had been on the drug an unknown duration, but at least exceeding a year. The temperature range was a mean of 39.6° C with the maximum of 41.6°C. The fever was hectic (intermittent or remittent fever with a difference of more than 1.4 degrees between highest

TABLE 14

COURSES OF DRUG FEVER
PMH AND DVAMC

Total patients 43 Episodes 50

Antimicrobial Agents (29)	Days to Fever	Other Drugs (21)	Days to Fever
Penicillins 9	1,2,2,3,3,10,12,14,30	Diphenylhydantoin 9	18,21,23,30,30,41,43,56,60
Methicillin 6	12,14,15,18,18,30	Methyldopa 2	2,7
Cephalosporin 5	½,½,½,½,2	Iron Dextran 2	1,1
Sulfonamide 3	1,3,5	Barbiturates 1	7
Tetracycline 2	5,8	Benztropine 1	365
Colistin 1	7	Halothane 1	1
Lincomycin 1	9	Iodide 1	4
PAS 1	10	Propylthiouracil 1	13
Vancomycin 1	½	Quinidine 1	10
		Salicylate 1	½

TABLE 15

DRUGS THAT CAUSE FEVER (adapted from 55)

Pyrogen Effect	Thermoregulation Alteration	Hypersensitivity Common	Hypersensitivity Occasionally	Unknown Mechanism Common
Amphotericin B	Cimetidine	Cephalosporins	Allopurinol	Asparaginase
Bleomycin	Cocaine	Methyldopa	Azathioprine	Barbiturates
Streptokinase	Atropine	Penicillins	Hydralazine	Propylthiouracil
		Phenytoin	Iodides	Salicylates
		Procainamide	Isoniazid	Vancomycin
		Quinidine	Nitrofurantoin	
		Sulfonamides	Rifampin	
			Streptomycin	

and lowest values) in 24, remittent (variable but constantly elevated daily temperature) in 17 and intermittent (fever with temperature returning to normal daily) in six. Chills or rigors were present in 26, headache in 16, and myalgias in 16. A rash was detected on physical examination in 20 patients of whom 13 had a papular eruption and one was erythematous. Hypotension was noted in six patients and serositis in four. The white blood cell count was variable, ranging from 2,200 to 37,000 with a mean of 12,000.

Elevated eosinophil count (exceeding 400/mm^3) was detected in 18 patients, all of whom developed fever following a drug which causes fever by hypersensitivity or immunological mechanism. (55) The eosinophilia was more likely to occur in those receiving diphenylhydantoin (7 out of 9 cases). (56) Liver function abnormalities were noted in fifteen cases, particularly in those having fever due to dephenylhydantoin; the values returned to normal in all cases after the drug was discontinued. The patient with fever due to quinidine did not have liver function abnormalities, although drug fever with this drug is reported with a form of granulomat hepatitis. (57) Renal function abnormalities were reported in five, of whom three returned to normal.

The drug fever increased the estimated length of hospital stay by nine days (mean). More than five blood cultures were drawn per episode and an average of 2.85 x-rays were done as part of the workup for fever. Fifteen patients had lumbar punctures and nine had biopsies (including two liver biopsies). A total of 23 were treated with antibiotics empirically, 37 received antipyretics and nine patients received steriods for fever. Two patients died, one following halothane reexposure and another developed acute renal failure following methicillin.

Adverse reactions are reported to occur in about 10% of hospitalized patients and 2.5% of outpatients receiving drugs. (58) Fever as a prominent manifestation occurs in approximately five percent of these reactions of .5% of reactions occurring in hospitalized patients. (59) Although any drug can be responsible, certain medications are much more likely to result in fever. The common ones which result in a hypersensitivity reaction, include the principle ones reported in this series, such as penicillin derivatives, diphenylhydantoin, methaldopa and sulfonamide. Although cephalosporins are listed as only occasional causes of drug fever, due to the widespread use of these agents, they can be considered common causes based on another review of drug fever and this report. (60) The analysis of these cases indicates that few generalizations can be made regarding the onset of fever in relation to administration of the drug or the type of fever pattern elicited. It is generally thought that fever typically appears on the seventh to tenth day of therapy, but this only occurred in 20% of the episodes at PMH and DVAMC. (55) The clinical presentation with chills, headache, myalgia, hectic fever, and leukocytosis and hypotension may obviously mimic a septic process in the hospital, such as gram negative sepsis. This was uppermost in the minds of house officers caring for these patients, since at least half received antimicrobial therapy for the persistent fever. Unfortunately other manifestations of drug hypersensitivity such as skin rash, serositis or eosinophilia are present in fewer than half of the cases. Removal of the drug with rechallenge is one of the recommended approaches to prove that the drug was responsible for the fever. The fact that four of the five patients receiving cephalosporin developed fever within two days in those with a history of

previous drug fever to a β-lactam indicates that drug fever should be considered as a contra-indication to treatment with another β-lactam. Obviously no one would consider rechallenge with halothane or methicillin - in fact these deaths are partially responsible for these two no longer being recommended at our institution. A number of drugs, including some responsible for drug fever in this series, cause fever by unknown mechanisms not related to hypersensitivity, including barbiturates, salicylates and propylthiouracil. (TAble 15) Other drugs can be responsible for fever due to effects on thermal regulation, including mechanisms that work centrally, such as amphetamines, cocaine, and cimetidine and those that work peripherally by decreasing sweating, such as atropine-like compounds (benztropine contains atropine). Other drugs result in fever due to a direct pyrogen effect including amphotericin-B, bleomycin and streptokinase. Finally, certain drugs may produce fever following inflammation at the site of delivery by creating a sterile abcess. This was noted particularly when Kanamycin was the popular amninoglycoside which was administered intramuscularly. In contrast, administration of streptomycin most likely results in fever due to hypersensitivity. Intravenous administration of drugs such as vancomycin may also be responsible for fever via phlebitis, a common cause of fever in hospitalized patients but only an indirect result of the drug they are receiving via the intravenous route.

The mechanism for the development of drug fever, especially with those drugs which induce hypersensitivity remains unknown. It is considered by some to be an idiopathic reaction to penicillin since no specific immune mechanism has been identified. (61)(Table 16) Hence, these reactions cannot be predicted by pretreatment skin tests for Ig E antibody. If the fever were manifestation of serum sickness, in association with serositis and involvement of the skin and kidney, then the fever would represent a type III reaction due to the presence of IgG and IgM antibodies. (61) Drug fever could follow the formation of immune complexes which could be phagocytized by macrophages, resulting in the release of endogenous pyrogen. (60) However, the affinity constants for antigen-antibody reactions has an inverse relationship to temperatures below 37° centigrade; in fact generation of complexes results in manifestations more frequently brought on by cold rather than by elevated temperature; and with lesions over external surfaces of the extremities. (62) Hence, the cause of drug fever remains a mysterious response of the host to the inciting drug. Since the onset and manifestations of totally unpredictable, clinicians must be alert to a drug being responsible for patient's fever, in an outpatient or in hospitalized patients. Specifically antimicrobial agents given for febrile illnesses must be considered as potential candidates.

TABLE 16

CLASSIFICATION OF REACTIONS TO PENICILLIN (61)

Type of reaction and immune mechanism	Clinical Syndrome
I. IgE antibody	Anaphylaxis Laryngeal edema Early onset of urticaria(72 hr)
II. Cytotoxic antibody	Hemolytic anemia
III. Antigen-antibody complexes	Serum sickness
IV. Delayed hypersensitivity Idiopathic	Contact dermatitis Maculopapular drug eruptions Nephritis Late onset of urticaria Fever Eosinophilia

TABLE 17

Unusual reactions with antimicrobial agents

Vancomycin	"Red Neck" Syndrome (63) Hypotension (64)
Doxycycline Minocycline Tetracycline	Photo sensitivity (65) Slate gray discoloration (66) Renal failure enhancement (67,68) Pancreatitis (67)

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