Ins and Outs of Antimicrobial Therapy - 1978

Medical Grand Rounds
December 21, 1978

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I. Aminoglycosides: Are they the solution or the problem?

A. Serum levels of aminoglycosides: A matter of inequality

CP a 54 year old white male was admitted to the Veterans Administration Medical Center (VAMC) on 7/3/78 with a significant history of alcohol consumption and a two day history of fever, right sided pleuritic chest pain and cough productive of reddish sputum. On physical examination, he had a temperature of 104°F, blood pressure of 110/75, tachypnea and obtundation. Chest examination showed dullness to percussion, with coarse rales and E to A changes in the right lower lungfields. He also had hepatomegaly and was jaundiced. On admission, he had a white blood count of 1,600/mm^3 with 12% polys, 13 stabs, 51 lymphs, 1 mono, 11 myelocytes and 12 metamyelocycytes. Hct was 37, bilirubin was 16.2 g/dl and SGOT was 255. Chest x-ray showed right lower and middle lobe pneumonia. Sputum gram stain showed gram positive diplococci and small gram negative rods. He was initially begun on penicillin 12,000,000 units a day and gentamicin 60 mgs q. 8 hours (1 mg/kg). Blood cultures were positive for *Pseudomonas aeruginosa*. He had a very stormy hospital course, becoming hypotensive soon after admission, and required dopamine administration after BP failed to respond to fluid administration (monitored with a Swan-Ganz catheter). Since the lumbar puncture results were negative, he was treated with lactalose for presumed hepatic encephalopathy with eventual improvement in mental status. He continued to have temperature elevations to 102°F during the first two weeks of hospitalization although repeat blood cultures were negative for Pseudomonas. Since gentamicin blood levels on the 7th hospital day showed peak values below 1 µg/ml (Table 1), the dosage was increased to 80 mgs q. 8 hours (1.3 mg/kg). However peak levels three days later were still less than 2 µg/ml and creatinine remained less than 1 mg/dl.

TABLE 1

COURSE AND THERAPY OF PATIENT WITH PSEUDOMONAS PNEUMONIA

DATE	7/10	7/14	7/18	7/24	8/2
TEMPERATURE	102°F	102.2°F	102°F	101.5°F	100
GENTAMICIN (q. 8 hrs)	60 mgm	80	100	100	-
TROUGH (µg/ml)	0.9	0.9	0.9	2.6	-
PEAK (µg/ml)	0.9	1.9	3.2	4.5	-
CREATININE (mg/dl)	0.6	0.5	0.6	1.0	2.6

The dosage of gentamicin was then increased to 100 mgs q. 8 hours (1.7 mg/Kg 8 hours) with a resulting increase in peak levels above 3 µg/ml. Carbenicillin, 5 gms q. 4 hours, to which the organism was sensitive, was also added on the 6th day but he developed a macular papular eruption on the 9th day so the drug was discontinued. He received a 4 week course of gentamicin with eventual clearing of the pneumonia although residual radiological changes persisted. During the last week when his temperature was in the range of 100-101°F, repeat gentamicin levels showed the trough level had risen to 2.6 µg/ml and peak of 4.5. Creatinine at discontinuation of therapy was 1.3 mg/dl but 6 days later was 2.6 mg/dl.

This patient presented with an unusual organism causative of a community-acquired pneumonia (1). This organism is a rare inhabitant of the oropharynx of alcoholic patients (2%), who commonly harbor gram-negative bacilli (35%) (2). This case illustrates the difficulties of maintaining adequate therapeutic serum levels of gentamicin in a febrile patient with a serious infection. Previous studies in animals and in humans have shown that fever reduces the peak serum level and shortens the half-life of gentamicin, so that adequate serum concentrations (5-10 µg/ml) are difficult to achieve with the usual dosage of 1.5 mg/kg every 8 hours (3, 4). In addition, it has not been possible to maintain adequate serum concentrations in patients with burns with the usual dosage and interval of administration of gentamicin; in fact, it has been recommended that the interval of dosing be decreased to 4 hours in such patients (5). Patients who have cystic fibrosis and pseudomonas infection also require increased doses of aminoglycosides to maintain therapeutic levels (6). Other factors that may lower the serum level of aminoglycosides include high extracellular fluid volumes and obesity, especially if the dosage is calculated on lean body weight (4, 7). It has been recommended that the initial dosage calculations in obese patients be based on ideal weight plus 40 percent of the adipose mass since aminoglycosides are not totally excluded from adipose tissues (7). Conversely, hypoxemia prolongs the half-life, perhaps due to effects on renal excretion (8).

Since alterations in the dosage of aminoglycosides may be required in the above situations, determination of peak serum values are recommended. Adequate serum levels are more likely if a loading dose of gentamicin or tobramycin is administered at 2.0 mg/kg followed by doses of 1.5 mg/kg and amikacin at 7.5 mg/kg (varying the frequency or dosage by prescribed formulae if patients have reduced renal function) (9). Some groups routinely measure peak levels (one hour after infusion) 24 hours after initial dose and alter subsequent doses and maintain a plasma level of 5-10 µg/ml of tobramycin, 5-10 µg/ml of gentamicin or 20-40 µg/ml of amikacin, then reducing the dose later in the course as the patient responds (10). If the patient with bacteremia remains febrile, as in our case,in addition to evaluating the patient for persistent bacteremia or abscess, serum levels certainly should be used to guage the adequacy of the drug (peak levels) and the levels predictive of nephrotoxicity (trough levels > 2 µg/kg). The concept of maintaining adequate blood levels in febrile patients has been given further impetus by the experimental studies of Ruderman and Mackowiak who showed enhanced bactericidal activity of gentamicin for pseudomonas and *E. coli* at elevated temperatures (unpublished observations).

B. Nephrotoxicity of aminoglycosides: A side effect or the main event.

Nephrotoxicity with aminoglycosides is not an infrequent event. Cumulative data indicates that the incidence is between 2 to 3%, but the frequency has been found to be 8-10% of patients in whom adequate serum levels of gentamicin and amikacin were monitored and even up to as high as 40% in seriously ill adult patients (10-12). Nephrotoxicity occurs late in therapy (mean date of onset: day 10) although a significant proportion have a continued rise in creatinine up to 9 days after cessation of therapy (as was noted in our case) (10). Since it has been shown that peak and trough serum levels tend to rise with time of therapy, these observations underscore the need to reassess the dosage of aminoglycosides after 5-7 days, especially if the patient has become afebrile on therapy (13). These rising peak or trough levels by day 7-10 of

therapy may not be the cause of nephrotoxocity but rather the consequence of decreasing glomerular filtration (10). In most cases, the serum creatinine returns to normal after discontinuation of gentamicin. However, permanent pathologic changes have been noted in experimental studies (Cronin, R).

Either ototoxicity or nephrotoxicity may occur even if peak levels are kept below 10 µg/ml for gentamicin or tobramycin or below 40 µg/ml for amikacin (11). Thus, these toxic manifestations represent a substantial risk of therapy with these agents. In experimental studies of aminoglycoside-induced toxicity, nephrotoxicity reaches its peak at 14 days of therapy and improvement in renal function occurred after that time even if the aminoglycoside was continued (14). Hence, one should not fear the continued use of aminoglycosides in patients with significant renal function impairment (even if that impairment has been produced by aminoglycoside), if the administration of aminoglycoside is indicated. Conversely, if the patient is <u>not</u> having significant abnormalities, as positive cultures in afebrile patient, do not use these toxic drugs. Insufficient observations are available in humans to determine if any of the recently approved aminoglycosides are less nephrotoxic than gentamicin. Tobramycin has been shown to be less nephrotoxic in the male rat, but no well controlled studies show similar finding in humans (14). We continue to utilize gentamicin as the aminoglycoside drug of choice and reserve tobramycin for infections proven to be due to pseudomonas (since tobramycin usually has a lower minimum inhibitory concentration (MIC) for this organism) (15). Amikacin is indicated for those patients with hospital-associated infections with gentamicin-resistant organism (11).

C. Combinations of aminoglycoside with other antimicrobial agents

1. Pseudomonas osteomyelitis in patient with hypogammaglobulinemia: a rarity in a rarity

LB, a 63 year old white male, had been followed in GI clinic for diarrhea and hypogammaglobulinemia. In 1960, he began to have frequent episodes of pneumonia and bronchitis requiring repeated hospitalization. In 1973, work up for recurrent diarrhea showed normal stool fat, D-xylose and Schilling tests, although serum B12 was low. Jejunal biopsy showed villous atrophy and lymphangiectasia. Immunoglobulin levels showed IgG: 196 mg/dl (normal 800-1800), IgA 64 mg/dl (normal 90-450) and IgM 188 mg/dl (normal 60-260). He also failed to respond to typhoid vaccine with a normal antibody response (fourfold rise) He was begun on monthly gammaglobulin at 0.6 ml/kg or 45 ml per month which prevented further episodes of pneumonia requiring admissions. He continued to have recurrent bouts of diarrhea.

In February 1978 he noted pain in his left hip, which gradually increased in severity over the next few months. He was admitted to VAMC where the only positive finding was a positive bone scan with enhanced uptake in an area of the left greater trochanter. ESR was 33 mm/hr, but white count was normal. He was thought to have trochanteric bursitis and the area was injected with depomedrol. He received transient relief, but the pain returned, so he was then admitted for surgical biopsy. Upon removal of a small section of bone, purulent material was noted, which grew *Pseudomonas aeruginosa*. Pathological examination of the bone revealed chronic inflammatory tissue. He was begun on tobramycin 1.5 mg/kg q 8 hours and ticarcillin 3 gms q 4 hours. Over the course of the 6 weeks of therapy, his ESR fell to 11 mm/hr and the patient's pain diminished. He was discharged to be continued on his monthly injections of gammaglobulin.

This patient represents an adult with common variable hypogammaglobulinemia which has variable onset and expression (Table 2). This condition should be suspected in patients with recurrent pulmonary infections more frequently than every 6 months (18). Gastrointestinal manifestations, may predominate with symptoms of diarrhea and steatorrhea, and a variety of defects are seen on biopsy of small intestine (17). Search should be made for *Giardia lamblia* since this agent may be responsible for steatorrhea and treatment with metronidazole will be curative. As illustrated by this case, the frequency of pulmonary infections are diminished by monthly gammaglobulin injections, although gastrointestinal manifestations are not affected. Bone infections and infections with pseudomonas are infrequent in this condition (17).

TABLE 2

CHARACTERISTICS OF COMMON VARIABLE HYPOGAMMAGLOBULINEMIA (16, 17)

Recurrent pulmonary infections within 6 months

Frequent gastrointestinal symptoms

Ig levels decreased, but not extremely low

Fail to respond to antigen (typhoid, tetanus)

May have defective delayed hypersensitivity response

Pulmonary infections respond to gamma globulin

Risk of malignancy (GI, lymphoma) increased after 10 years

It is paramount first to establish the etiology of the bone infection by recovery of the organism from an operative specimen (19). Sinus tract cultures from patients with chronic osteomyelitis do not reliably predict the infecting organisms. The principal antecedent factors in patients with pseudomonas osteomyelitis have been surgery or breach of the skin in the area near the infected site (20). Hence, we must consider that the steroid injection was a predisposing factor in this individual. Steroid injections have been frequently incriminated in pyogenic arthritis (21). Heroin addicts have a propensity for pseudomonas osteomyelitis of the sternum with arthritis of the sternoclavicular joint (22). This case illustrates a situation in which an aminoglycoside should be given with another agent to treat an infection with an organism susceptible to the aminoglycoside. Both calcium and magnesium increase the minimum inhibitory concentrations of gentamicin for *Pseudomonas aeruginosa* but not for *Escherichi coli* (23). Those studies further showed that the binding of radioactively-labeled gentamicin to pseudomonas was impaired in the presence of divalent cations. Because of these experimental observations and single case reports indicating aminoglycoside treatment-failures of bone infection, the therapy of choice for patients with pseudomonas osteomyelitis and septic arthritis would be the combination of carbenicillin or ticarcillin with an aminoglycoside (20, 22). The recommended duration of treatment for proven pseudomonas bone infections is six weeks of an aminoglycoside with either carbenicillin or ticarcillin. Since the susceptibility testing of pseudomonas has shown lower minimum

inhibitory concentrations (MIC) with tobramycin than with gentamicin, then this agent is the treatment of choice for bone infections with *Pseudomonas aeruginosa* (15). Since the achievable MIC levels for carbenicillin (5 gm) and ticarcillin (3 gm) are equivalent for recommended dosages, the lower sodium administration with ticarcillin represents an advantage.

2. Pseudomonas endocarditis: Additional cost of heroin addiction

Another situation in which combination therapy with aminoglycoside and another agent has resulted in medical cures is Pseudomonas endocarditis (24) Endocarditis in heroin addicts with *Pseudomonas aeruginosa* has variable incidence in the U.S., and we (PMH and VAMC) have seen only one case in Dallas. He was a drug user who has required consecutive course at each hospital of tobramycin and ticarcillin. Adequate serum killing activity were achieved during both treatment courses. Medical management with combination therapy of an aminoglycoside and carbenicillin has been successful in a small number of cases, although surgery has been required in some bacteriologic failures (24). Dosages of gentamicin or tobramycin up to 8 mg/kg/day have been utilized in combination with either carbenicillin or ticarcillin to achieve recommended serum killing power. Ticarcillin would have the advantage of lowered sodium administration; however, if the patient develops symptoms of congestive failure, valve replacement should be anticipated since surgery significantly improved survival in patients with moderate or severe failure (25).

3. Enterococcal endocarditis: tried and true versus new Boston view

JC a 33 year old black male heroin user since 1966 had maintained his habit since 1966 with confidence since he used a new needle each time although he did share it with his wife and girlfriends. Two weeks prior to admission, he noted a shaking chill which he attributed to withdrawal symptoms. At this time, he also noted hematuria and pyuria but these features cleared over the next week. He finally presented to the VAMC detoxification unit because his nerves were bothering him and his feet hurt. On admission, he had a temperature of 102°F, a grade IV/VI diastolic decrescendo murmur present over the entire precordium loudest at the lower left sternal border and a grade II/VI systolic ejection murmur at the lower left sternal border. His EKG showed left ventricular hypertrophy and an echocardiogram showed normal motion of the aortic and mitral valves without vegetations, and a slightly dilated left ventricle. Blood cultures were positive for enterococcus which was sensitive to Streptomycin at 500 µg/ml. He was initially begun on penicillin G 12,000,000 units a day, gentamicin 120 mgs q. 8 hours and methicillin 12 gms a day, but when the sensitivities for streptomycin returned, he was switched to streptomycin 1 gm every 12 hours and the methicillin was discontinued. He achieved serum killing activity one hour after penicillin and streptomycin at a 1:8 dilution of serum. He became afebrile promptly on institution of antimicrobial therapy. He had tachycardia without dyspnea with exercise and occasional runs of PVCs (related to stressful conversations with his wife and girlfriends). EKG and echocardiogram showed no change during the four weeks of therapy. Urinalysis revealed pyuria on admission, but a midstream urine showed no white cells and no casts. Thus, his pyuria was likely secondary to asymptomatic non-gonococcal urethritis rather than a manifestation of immune complex disease since his latex fixation test was negative.

Enterococcal endocarditis in heroin users is highly variable from city to city (26). This organism attacks the valves on the left side of the heart. This patient was not considered a candidate for cardiac catheterization nor surgery since his aortic insufficiency was stable during his hospital course and he showed no evidence of congestive heart failure (25). He was treated with penicillin G and streptomycin since the organism was susceptible to < 2000 µg/ml of streptomycin and thus was susceptible to the synergistic action of the two antibiotics (27). Although Moellering and associates found many isolates (including blood) of enterococci resistant to streptomycin, there are few reported failure with penicillin and streptomycin. We have determined susceptibility on organisms from cases in the Dallas area and most isolates from patients with endocarditis were sensitive to 2000 µg/ml of Streptomycin or less. Serum killing powers should be done on antimicrobial therapy to confirm that synergism is present: If dilutions of serum of 1:8 or greater show killing. Gentamicin is synergistic with penicillin for organisms resistant to streptomycin (28, 29). Kanamycin and amikacin are not synergistic with penicillin for streptomycin-resistant enterococci since these organisms have both streptomycin adenylyltransferase and neomycin phosphotransferase enzymes, which phosphylates both kanamycin and amikacin, resulting in resistance of enterococci to antibiotic synergism (Table 3) (29).

TABLE 3

High-Level Aminoglycoside Resistance, Aminoglycoside-Modifying Enzymes, and Resistance to Antibiotic Synergism among Isolates of S. faecalis* (29)

	Clinical isolates		Trans-conjugant strain
	Resistant	Sensitive	
High level resistant to			
Streptomycin	+	-	+
Kanamycin	+	-	+
Aminoglycoside-modifying enzymes			
Streptomycin adenylyl-transferase	+	-	+
Neomycin phosphotrans-ferase	+	-	+
Resistance to antibiotic synergism			
Penicillin-streptomycin	+	-	+
Penicillin-kanamycin	+	-	+

* High-level resistance equals minimal concentration > 2,000 µg/ml.

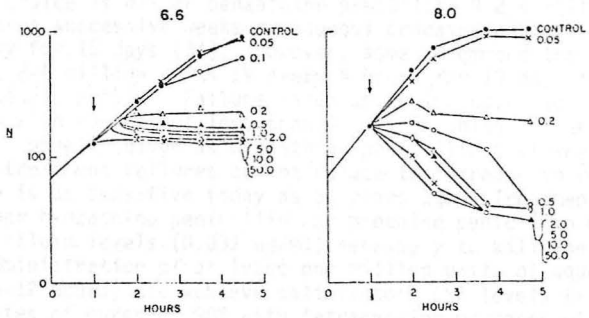
II. Penicillin derivatives: the oldest and the newest.

A. So you thought penicillin G killed bacteria?

"On the basis of these findings, we propose a new hypothesis for the mechanism of penicillin-induced lysis of bacteria. It is suggested that inhibition of cell wall synthesis by any means triggers bacterial autolytic enzymes by destabilizing the endogenous complex of an autolysis inhibitor.... and autolytic enzyme." A. Tomasz and S. Waks (30).

Penicillin binds to one of 6-8 specific binding protein. Different penicillins bind to different proteins, thus synergism of penicillin and other derivatives (mecillinam) is possible because they bind to different binding proteins. The study of the mechanism of action has been made possible by the study of mutants. Penicillin inhibits both the wild type and mutants at the same concentration but conditions for lysis vary. These mutants are penicillin-tolerant: they are inhibited by penicillin but not killed by lysis (31). Lysis is temperature and pH dependent, so by adjusting growth media, the primary effects of penicillin can be separated from the secondary ones (Figure 1). Hence, at pH 6, cloxacillin inhibits growth, but penicillin-lysis doesn't occur, as it does at pH 8.0.

FIGURE 1 (31)



Effect of cloxacillin on cultures of *B. subtilis* 168 growing at pH 6.6 and pH 8.

Penicillin inhibits activity of a transpeptidase irreversibly which probably results in inhibition of growth. A secondary effect is the release of a murein hydrolase which is present in the cell wall but the activity of which is normally suppressed. This hydrolase then degrades preformed cell wall, resulting in lysis. In pneumococcus, the inhibitor of autolysis is the complex lipoteichoic acid (Forssman antigen) which leaks into the medium after addition of penicillin. Organisms which lack murein hydrolase (*S. sanguis* and *S. pyogenes*) do not undergo lysis although *S. pyogenes* rapidly loses viability in presence of penicillin whereas *S. sanguis* is not killed (32). [Is this why streptococcal endocarditis responds best to treatment with penicillin and streptomycin (Tompsett)?]. Cell lysis can be prevented not only by adjusting the pH of

growth medium but also by changing media components or concentrations of MG^{2+} (33).

B. Has penicillin G lost its touch?

1. Neurosyphilis. WN was a 48 year old black male, with a long history of alcohol abuse, who presented with a two week history of confusion and personality changes. Neurological examination on admission was negative save for organic psychosis. EEG showed mild to moderate diffuse slowing consistent with a metabolic encephalopathy. Skull series, brain scan, B12 and thyroid functions were within normal limits. He was begun on Haldol 5 mgs bid without significant change in psychosis. A VDRL was reported back as positive at a 1:64 dilution of serum with a positive FTA. Cerebrospinal fluid contained 27 WBCs/mm^3 with 24 lymphocytes, glucose of 106 mg/dl compared to a blood glucose of 261 mg/dl, protein of 98 mg/dl, a negative cryptococcal antigen, and a VDRL positive at a CSF dilution of 1:4. He was transferred to medical service where he was begun on a 10 day course of aqueous penicillin G, 1,000,000 units intramuscularly twice a day. His confusion and delusional symptoms improved and his behavior was nearly back to normal at time of discharge one month later. A repeat CSF examination after therapy showed 5 mononuclear cells and a protein of 71 mg/dl. He was discharged to return in 3 months for a follow-up lumbar puncture.

Considerable controversy exists concerning the appropriate therapy for neurosyphilis. The recommended CDC treatment schedule indicates that the treatment of choice is either benzathine penicillin G 2.4 million units IM weekly for three successive weeks or aqueous procaine penicillin G, 600,000 units IM daily for 15 days (34). However, some recommend the use of crystalline penicillin G, 2-4 million units IV every 4 hours for 10 days in patients with symptomatic neurosyphilis. Failure rates up to 10% have been noted with treatment regimens with courses of less than 4 million units of penicillin to 9 million units, usually given as benzathine penicillin G at weekly intervals (35). These treatment failures do not relate to increase in resistance since the treponeme is as sensitive today as 30 years ago. Treatment failures result because neither benzathine penicillin nor procaine penicillin G achieve adequate cerebrospinal fluid levels (0.031 μg/ml) necessary to kill the treponeme (36, 37). Administration of at least one million units of aqueous penicillin G IV (every 6-12 hours) did achieve satisfactory CSF levels (> 0.3 μg/ml). Successful rates of cures of 90% with tetracycline or doses of penicillin inadequate to achieve spirocheticidal levels probably occur because the infection is a perivascular infection; consequently, in a majority serum levels of oral or intramuscularly administered drugs may be sufficient to kill the treponeme in blood vessels (35, 38). Appropriate therapy to cure all cases of neurosyphilis especially those with treponemes in CSF will require higher dosages than the recommended dosages used to treat late latent syphilis without neurological involvement (39).

Hence, a high index of suspicion should be continued so as to detect patients with symptomatic neurosyphilis. Patients with neurosyphilis most commonly present today with adult-onset seizures, abnormal pupillary findings, or recent onset of psychiatric symptoms (40). Individuals with these findings, regardless of peripheral VDRL, should have an examination of cerebrospinal fluid with serological test for syphilis. If pleocytosis is present and VDRL

is positive, or if serum FTA is positive with pleocytosis (> 5 leukocytes/mm^3), then therapy with parenterally administered aqueous penicillin G should be undertaken, giving at least 2 million units a day for 10 days. This dosage has been curative in patients who failed to respond to 9 million units as benzathine penicillin (37, 38). If the patient is allergic to penicillin, tetracycline 500 mg 4 times a day (prior to meals) for 30 days is the treatment of choice and achieves cure rates of 90%+ (38). Examination of CSF should be performed at completion of therapy and at 3 months after therapy. Relapses or failures to respond to therapy (more likely in patients with general paresis) will be demonstrated by the failure of the cell count to return to normal or failure of the CSF serology to fall. Most treatment failures will be seen within 3 months of treatment but patients should be followed clinically for at least 2 years and repeat CSF exams done if any change in symptoms occurs.

2. Treatment of anaerobic pneumonia. Does V equal G?

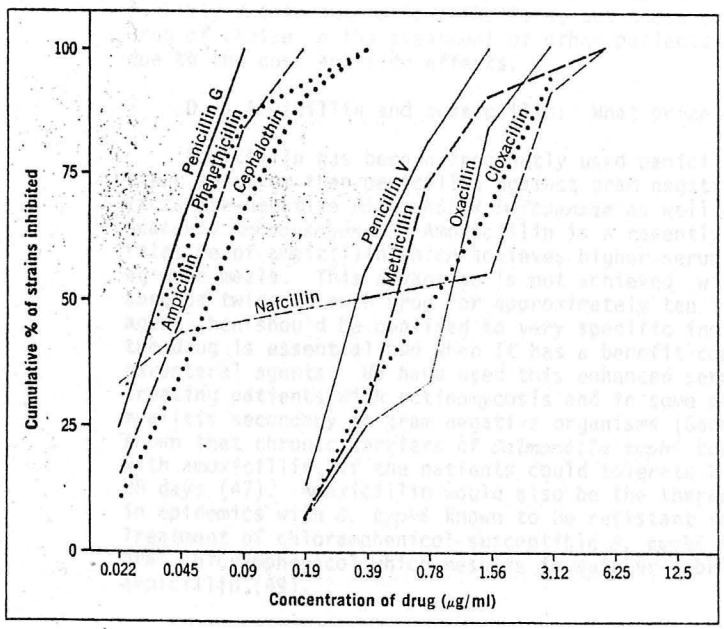
Penicillin G is the treatment of choice for community-acquired lung abscess of necrotizing pneumonia due to anaerobic organisms. Although the generally accepted therapy is to administer parenteral penicillin G 4-6 million units per day, a controlled study indicated that orally administered penicillin G 750 mg 4 times a day before meals was as efficacious as penicillin (41). Most patients given either oral or parenteral penicillin became afebrile within 10 days of therapy and showed equivalent decrease in size of cavities. Total disappearance of the cavity required 4-6 weeks of therapy for the majority although some required up to 3 months for the x-ray to return to normal. Satisfactory levels are absorbed with oral penicillin G in fasting patients to achieve 0.8 μg/ml, which is effective against the great majority of causative organisms (Table 4 (42). Orally administered penicillin V is not a satisfactory alternative since penicillin V is only 1/4 as active as penicillin G. (Figure 2). Ampicillin would be an appropriate alternative to penicillin G although administration of this drug is associated with greater intestinal and skin side effects. Although *Bacteroides fragilis* may be isolated from transtracheal or pleural fluid cultures from patients with anaerobic infections, treatment with clindamycin or chloramphenicol does not appear to be essential in most anaerobic pulmonary infection. Since erythromycin is active against a majority of causative organisms, it would be regarded as an alternative agent for individuals allergic to penicillin (Table 4) (42). Cephalothin or cephalexin are not as effective as penicillin, atlhough cefoxitin would cover most causative organisms (44). Clindamycin should be considered in those patients who continue to have clinical activity and temperature elevations more than 10 days after institution of penicillin therapy or in those patients in whom *Bacteroides fragilis* is isolated from the blood stream. Tetracycline would be slightly less effective and other derivatives are expensive. Hence, a number of alternative agents are available for treatment of anaerobic pneumonia (42-44).

TABLE 4

SUSCEPTIBILITY OF VARIOUS ANAEROBIC BACTERIA TO VARIOUS ANTIBIOTICS (42-44)

ANTIBIOTIC	Penicillin G		Carbenicillin	Tetracycline	Minocycline	Chloramphenicol	Clindamycin	Erythromycin	Cephalothin	Cefoxitin
MIC (μg/ml) to inhibit	0.8	6.2	100	3.1	3.1	6.2	3.1	3.1	12.5	32
Peptostreptococcus	98	100	100	73	-	100	100	88	99	100
Fusobacterium	100	100	100	89	100	100	100	95	78	100
Clostridium perfringens	97	100	100	82	80	100	100	100	100	100
Clostridium sp.	100	100	91	94	88	100	94	100	92	52
B. melaninogenicus	65	86	100	79	75	100	100	96	93	100
B. fragilis	1	7	96	36	66	98	100	92	4	100

FIGURE 2.



Activity of various penicillins and cephalosporins against *B. melaninogenicus* (Finegold SM: Infections due to anaerobes, Med. Times 96:174, 1968)

C. Carbenicillin and ticarcillin: Are they the answer?

Carbenicillin has been the treatment of choice along with aminoglycosides for febrile episodes in leukopenic patients following chemotherapy. It is efficacious for non-hospital-associated gram negative organisms including *Pseudomonas aeruginosa,* but the drug is not as effective against hospital-associated strains (less than 30 percent of blood culture isolates sensitive). Major limitations include cost and side effects (hypokalemia and bleeding in renal failure). The drug would only be used in patients with normal white cell counts as combination therapy with an aminoglycoside for pseudomonas bone infections and endocarditis.

Ticarcillin, a recently introduced agent, has similar spectrum and side effects as carbenicillin but has one advantage in that slightly smaller dosages are required to achieve equal serum concentrations with similar minimal inhibitory concentrations against susceptible bacteria (45). This would be moderately beneficial for individuals with congestive failure since the daily sodium administered with ticarcillin (2.2 gram) is less than with carbenicillin: (3.3 gram/day). Synergism with aminoglycosides for pseudomonas appears to be equal. Choice between these two agents then would rest upon the relative cost to the hospital pharmacists of the two drugs. Both carbenicillin and ticarcillin are active *in vitro* against *Bacteroides fragilis* at levels that can be achieved in humans and clinical studies have indicated that these drugs may be efficacious in anaerobic infections including those in which *B. fragilis* is a pathogen (46). However, patients with anaerobic infections must be watched carefully since failures could occur if the organisms produce β- lactamase as occurred with penicillin G so that it failed to treat infections even when high levels were administered (43, 44). Hence, carbenicillin or ticarcillin would be reasonable agents in the leukopenic individuals with peri-rectal infections possibly due to anaerobic infections, but these agents would not be a primary drug of choice in the treatment of other patients with anaerobic infections due to the cost and side effects.

D. Ampicillin and amoxicillin: What price must the consumer absorb?

Ampicillin has been a frequently used penicillin derivative with a slightly wider spectrum than penicillin against gram negative bacteria, including beta-lactamase-negative *Haemophilus influenzae* as well as for infections with *Listeria monocytogenes*. Amoxicillin is a recently introduced antimicrobial relative of ampicillin which achieves higher serum levels even when administered with meals. This advantage is not achieved without cost since the patient absorbs twice as much drug for approximately ten times the cost. Use of this agent then should be confined to very specific indications when absorption of the drug is essential and when it has a benefit comparable to the use of parenteral agents. We have used this enhanced serum level to advantage in treating patients with actinomycosis and in some patients with chronic osteomyelitis secondary to gram negative organisms (Goodman). Recently it has been shown that chronic carriers of *Salmonella typhi* could be successfully treated with amoxicillin, if the patients could tolerate 2 grams 3 times a day for 28 days (47). Amoxicillin would also be the therapy of choice for typhoid fever in epidemics with *S. typhi* known to be resistant to chloramphenicol (48). Treatment of chloramphenicol-susceptible *S. typhi* is best accomplished with oral chloramphenicol which results in quicker febrile response than with ampicillin (49).

E. New cephalosporins: when is more less?

The most recently introduced cephalosporins are cefamandole and cefoxitin adding to an every increasing roll of these derivatives. Cefamandole is a parenteral cephalosporin which has significantly greater activity against gram negative bacilli, including enterobacter, Proteus and *H. influenzae*, than do the other cephalosporins (50). However, *in vitro* susceptibility testing must be done with a separate disk. It has not been evaluated in sufficient number of cases of staphylococcal endocarditis to be certain whether it would be appropriate therapy, although it was successful in non-bacteremic staphylococcal infections. It is not as active against *Staphylococcus aureus* as cephalothin, the cephalosporin of choice for serious staphylococcal infection. It has not been clearly established if hospital-associated gram negative bacteria are susceptible. Curiously, no investigators have compared it to other antibiotics nor separated the isolates by hospital-associated strains (51). This would be important to do before considering cefamandole for such infections since a very low percentage of hospital-associated positive blood cultures in 1977 at VAMC were susceptible to cephalosporins. Although cefamandole is active for up to 90% of *Enterobacteriaceae*, it is not as effective as aminoglycoside against Pseudomonas (McCracken, A). Toxicity appears to be similar to that of the other cephalosporins including phlebitis and transitory liver function abnormalities. Allergic reaction are higher in those with a history of penicillin allergy (52). The dosage also needs to be reduced if renal function impairment is present. Although it has been used successfully in the treatment of meningococcal meningitis, the drug has not been as successful for *H. influenze* meningitis (50) nor does it prevent Listeria meningitis (Sutker, W. and Tompsett, R). Hence, the drug is less toxic than aminoglycosides and more effective than other cephalosporins for gram-negative bacilli other than Pseudomonas. However, for unknown hospital-associated bacteremias, this agent would have to be combined with an aminoglycoside.

Cefoxitin is a semi-synthetic derivative of cephamycin C (a relative of the cephalosporins) with enhanced activity against anaerobic organisms including *Bacteroides fragilis* (Table 4) (44). It has also been shown to be efficacious in clinical studies and has been approved by the FDA for use in anaerobic infections with *Bacteroides fragilis*. This antibiotic is not as effective against staphylococcus or streptococcus as is cephalothin and it shares with the other cephalosporins lack of activity against Enterococcus (51). It is the only cephalosporin active against *Eikenella corrodens*, the causative organism in some infections following human or dog bites (53, 54). It should be considered a second-line agent for anaerobic infections if aerobic gram-negative organisms present are also sensitive to cephalosporins. Other cephalosporins are not effective in treatment of infections with *Bacteroides fragilis*; in fact, their use may predispose to infections with these organisms in certain circumstances. A recent VA Cooperative study on antimicrobial prophylaxis of colon surgery found that cephalothin failed to change the incidence of infections compared to placebo (30%) whereas orally administered erythromycin and neomycin significantly reduced the infection rates postoperatively (VA Cooperative Studies Prepublication).

The cephalosporins have very limited specific indications although they remain valuable second-line agents. Their use contributes significantly to excess hospital cost (55). Their gram-negative coverage is only valuable for community-acquired infections or for prophylaxis in certain particular situations (56). Their use in penicillin-allergic individuals must be restricted since allergic

reactions are increased four-fold in persons with a history of penicillin-allergy (52). Hence vancomycin is the alternative agent of choice in patients with endocarditis with a history of anaphylaxis or serious allergic reaction to penicillin. Cephalosporins in combination with aminoglycosides also enhances nephrotoxicity compared to frequency with methicillin and aminoglycoside (57).

III. New uses for old drugs, or the Second Coming for vancomycin and erythromycin.

A. Should vancomycin be given for every person with pseudomembranous colitis (PMC)

TW was a 57 year old male who presented with progressive weakness in all four extremities due to a spinal cord block at the C4-5 level, confirmed by myelogram. At surgery decompression was attempted, but no pathological diagnosis was made. He improved only slightly in the upper extremities postoperatively. He was given methicillin 1 gm q. 6 hours for 3 days, chloramphenicol 500 mgs q. 6 hours, for 13 days, decadron 4 mgs IV q. 6 hours for 25 days postoperatively. On the 24th postoperative day, he developed lower quadrant abdominal pain and bright red blood per rectum. Proctoscopy showed normal mucosa to 10 cms but above this the mucosa was friable, edematous and covered with yellowish-gray shaggy exudate. Over the next few days, the patient had a decrease in the frequency of stools from 6 to 2 per day. He was placed on NG suction for GI bleeding which cleared after which he was given a liquid diet. Proctoscopy 6 days after initial examination showed only slightly erythematous mucosa but no exudate or pseudomembranes. Since he continued to improve, he went to surgery for re-exploration of the C4-C5 area. At this time, a herniated nucleus pulposus was demonstrated as the cause of his quadriparesis. He gained strength postoperatively and was discharged on a walker with no further gastrointestinal difficulties.

This patient developed PMC following treatment with chloramphenicol. Although clindamycin has been the most frequently implicated agent associated with pseudomembranous colitis, any antibiotic other than erythromycin or vancomycin could cause this condition (58). PMC has been noted in decreasing order of frequency with clindamycin, ampicillin, cephalosporin, trimethoprim-sulfamethoxazole and very infrequently with penicillin G, penicillin V, chloramphenicol and tetracycline (Bartlett, JG).

Antibiotic-associated colitis has been shown to relate to a cytopathic toxin elaborated by *Clostridium difficile* (59). This organism is rarely noted in stools from normal individuals although it has been found in stool from neonates. Evidence that this toxin is responsible for pseudomembranous colitis was shown by the following: 1) presence of toxin in stool from 96% of cases of PMC and in approximately 6% of individuals with antibiotic-associated diarrhea but failure to detect toxin in stools from patients with ulcerative or neonatal necrotizing enterocolitis (Table 5); 2) neutralization of activity by pre-incubation with gas gangrene antitoxin or antitoxin to *Clostridium sordelli* and 3) recovery of toxin-producing strains of *Clostridium difficile* from stool from patients with PMC. No other strains of clostridia nor do strains of *Clostridia sordelli* normally produce toxin (the strain used to produce antitoxin did, thus giving anomalous finding). Patients with PMC have fever, blood in stools and fecal leucocytes. Diagnosis is made by visualization of yellowish plaques on proctoscopy (58). Most individuals with PMC improve when the implicated antibiotic is discontinued. Even those 1/3 who develop symptoms after the antibiotic is discontinued will respond to fluid management alone as did our case. The disease does not respond to gas gangrene antitoxin. If the patient

TABLE 5

CYTOTOXICITY ASSAY OF STOOLS (59)

Patient group	No. tested	Cytotoxicity test	
		Positive	Negative
Antibiotic-associated colitis			
Pseudomembranous colitis	27	26	1
"Nonspecific colitis"	16	6	10
Antibiotic-associated diarrhea	47	3	44
Neonatal necrotizing enterocolitis	24	0	24
Ulcerative colitis	10	0	10
Controls	65	0	65

is severely ill or if diarrhea persists for 3-4 days after discontinuation of the antibiotic, then vancomycin 500 mg p.o. 4 times a day should be administered. Its use in severe cases is accompanied by a decrease in fever in 1-2 days, a decrease in leukocyte count in 2-5 days and diminished frequency of stools in 3-10 days (Bartlett, J.G.) Repeat proctoscopy usually shows decrease in pseudomembranes within 5 days. The appropriate duration of therapy has not been established, but the drug is usually administered for 7 days. The major disadvantage of the drug is the high cost ($100/7 day course) as well as the obnoxious taste. On occasions, patients relapse after vancomycin is discontinued and retreatment has been required in these cases. Bartlett recommends that patients be placed on enteric isolation since hospital-associated outbreaks have occurred on some wards.

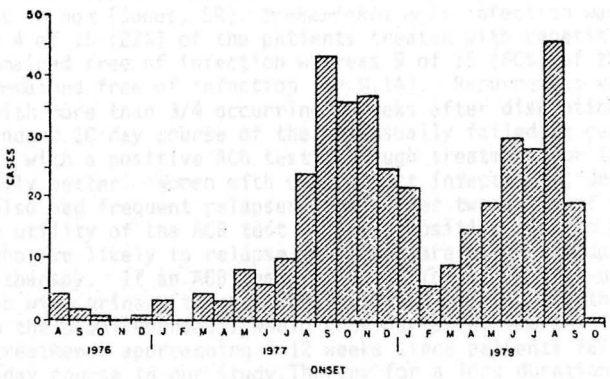
B. Old Legionnaires never die, they just need erythromycin.

LC, an 81 year old white male, member of an American Legion Post from Glen Rose, Texas, was admitted with a history of confusion and impaired memory for two months and nausea, vomiting and diarrhea for one week. When evaluated at another hospital he was noted to have cardiomegaly and to be jaundiced so he was treated for cardiac decompensation. When he failed to respond to digitalis and lasix he was referred to DVAMC. On admission, his temperature was 102^{o}F, his blood pressure was 150/80 and pulse was 150 and irregularly irregular. He was confused, disoriented, combative (and strong) but showed no localized neurological findings. Chest exam showed dullness at the right base and rales confined to the right posterior lungfields. Chest x-ray showed a right lower lobe alveolar infiltrate with redistribution in the upper lobes. White blood count was 11,500/mm^3 with a normal differential, creatinine was 2.0 mg/dl, phosphorus 2.3 mg/dl (normal 2.5 mg/dl), his SGOT WAS 179 units and his bilirubin was 3.4 mg/dl. He was initially begun on penicillin 10,000,000 units per day, gentamicin 1.5 mg/kg every 16 hours and erythromycin 2 gms per day by NG tube. His pulmonary infiltrates cleared over the next several days, he became afebrile after three days, but he continued to remain confused and disoriented. Brain scan

was normal, EEG showed no abnormalities and a cisternal puncture (lumbar puncture was not possible) showed no cells with a protein of 21 mg/dl. He became febrile again, developed right upper quadrant tenderness and a right pleural effusion but had a negative workup for fever, except for nonvisualizing gallbladder. He responded to penicillin and gentamicin for 10 days without any explanation for the second febrile episode save for possible urinary tract infection with "catheter fever." The Legionnaire's antibody test at 10 days was positive at a serum dilution of 1:32, and 1:64 at 24 days. (Not a significant rise so was not considered diagnostic).

Legionnaire's disease was suspected in this patient because he had the appropriate epidemiological history (elderly male who presents with pneumonia in the fall of the year), and systemic findings including unexplained encephalopathy, diarrhea, liver function abnormalities and metabolic derangements (hyponatremia and hypophosphatemia) (60, 61). Patients presenting with pneumonia in late summer and early fall are suspect since the peak incidence for sporadic cases and epidemics is in this period (Figure 3). In the past year microbiological isolates of the agent, now called *Legionella pneumophila* have been recovered from two cooling towers, two evaporative condensers and an Indiana Creek (62). Hence, the late summer pattern may relate to inhalation of contaminated air. The organism has very rarely been identified in sputum or transtracheal aspirate, although cultures of pleural fluid or lung tissue have been positive in immunosuppressed patients. Blood cultures are never positive. Serological confirmation is made on a significant (four fold) rise in titer from an acute serum obtained in first week of illness to a convalescent serum drawn at least 22 days after the onset of illness. Our patient did not qualify as a confirmed case.

FIGURE 3



Confirmed sporadic cases of Legionnaire's disease, by month of onset, United States, August 1976 through October 1978.

Since microbiological confirmation is infrequently achieved and since seroconversion is a late phenomenon, therapy is instituted based on a high clinical index of suspicion. Erythromycin has been highly successful in decreasing case fatality rates in epidemics of Legionnaire's disease, whereas penicillin, cephalosporin and aminoglycosides have had no effect on case-fatality rates. Improvement is noted within 24 hours with defervescence in 2 days in patients treated with erythromycin (60). The duration of therapy with erythromycin has been suggested to exceed 2 weeks (60). Although tetracycline has produced favorable response rates, the MIC values for tetracycline are relatively high and some tetracycline derivatives do not protect in experimental infections (63, 64). In contrast, rifampin appears to be highly effective both *in vitro* and in experimental infection. This drug has not been recommended due to concern about development of rifampin-resistant organisms in the community, which would limit its effectiveness for the meningococcus and mycobacteria. Rifampin would be the drug of choice if a suspect case failed to respond to erythromycin.

IV. Conditions with high rate of treatment failures

1. Poor response rates in upper urinary tract infection, or when is an upper a downer.

Recent studies in men and women indicate that upper urinary tract infections (UTI) respond poorly to course of antimicrobial therapy of usual (7-10 day) duration (65, 66). Men with recurrent UTI (more than 2 documented episodes in the past) were entered into a VA cooperative study to determine response rates to a standard 10 day course of therapy or a longer 12 week course with Trimethoprim/Sulfamethoxazole (Tmp/Smx). All men entered in this study had a positive antibody-coated bacteria (ACB) test consistent with upper tract infection. In addition 52% had evidence of prostate infection. Jones had shown earlier that men with positive ACB always had a bladder washout test which localized an infection to the kidney whether prostate infection was present or not (Jones, SR). *Escherichia coli* infection was present in 74%. Only 4 of 15 (27%) of the patients treated with repetitive 10-day courses remained free of infection whereas 9 of 15 (60%) of those treated for 12 weeks remained free of infection ($p = 0.14$). Recurrences were with the same organism with more than 3/4 occurring 4 weeks after discontinuing therapy. Thus a standard 10 day course of therapy usually failed to cure men with recurrent UTI with a positive ACB test although treatment for 12 weeks was not statistically better. Women with upper tract infection as defined by a positive ACB test also had frequent relapses (50%) after two weeks of therapy (65). Hence, the utility of the ACB test is for a positive test to predict those men or women who are likely to relapse and need careful follow-up after conventional course of therapy. If an ACB test is not performed, follow-up is essential in each person with urinary tract infection at one month. If the person fails to respond to the usual course, I would consider using Tmp/Smx for a longer duration of treatment, approaching 6-12 weeks since patients failed to respond to repeat 10-day course in our study. Therapy for a long duration would require informed consent and follow-up for side effects (hematological and liver function abnormalities) although use for 12 weeks was free of side effects in our study. Patients with frequent recurrences of UTI alternatively might be candidates for long term suppressive therapy with low dose Tmp/Smx or nitrofurantoin (67, 68). I prefer not to use either drug for longer than 6 months, consequently, I alternate low dose Tmp/Smx (½ tablet) with low dose nitrofurantoin (100 mg tablet) for 6 months in selected patients with symptomatic UTI.

2. Chronic osteomyelitis: Medical treatment for a surgical problem

Symptomatic recurrences of chronic osteomyelitis are manifested principally by recurrent episodes of purulent drainage from sinus tracts near the site of bone infection (69). These infections are particularly confusing therapeutically, since the longer the patient has been seen and treated, then it is less likely that cultures of sinus tract drainage will show the causative organism (19). When a comparison of cultures from operative specimens was made with sinus tract cultures, significant disparity was noted, particularly if sinus tract cultures were obtained late in the course (Table 6).

TABLE 6

RESULTS OF SEQUENTIAL SINUS-TRACT CULTURES (19)

Culture No.	No. of Cultures	Operative Pathogen, No(%)			
		Pure Culture	Preponderant Organism	Nonpreponderant Organism	Absent
1	35	17(49)	1(3)	6(17)	11(31)
2	28	9(32)	3(11)	6(21)	10(36)
3	22	7(32)	0(0)	7(32)	8(36)
4	16	4(25)	1(6)	3(19)	8(50)
5	13	0(0)	0(0)	4(31)	9(69)
6-21	69	3(4)	3(4)	7(10)	56(82)
Total	183	40(22)	8(4)	33(18)	102(56)

If *Staphylococcus aureus* was isolated on 3 consecutive occasions, it was predictive (78%) of actual infecting organisms, but isolation of *Pseudomonas aeruginosa* on 3 consecutive occasions was not predictive of the operative pathogen (Table 7). In fact, this organism was absent from all sinus tract cultures in 3 of 8 with pseudomonas bone infections. Hence, the major diagnostic test in a person with osteomyelitis is to obtain a culture from the bone or a clean needle aspirate of purulent material near the site of bone infection.

Once the microbial etiology has been established, appropriate antimicrobial therapy can be given. The majority of cases of chronic osteomyelitis are due to *Staphylococcus aureus* (60% in our series), for which the preferred treatment is cloxacillin 2-4 g. per day orally with the addition of probenicid for a minimum of six months (70). If the person has had multiple recurrences or has vascular disease, or is a diabetic, therapy may need to be continued indefinitely. If the infecting organism is a gram negative or anaerobic organism, then the most appropriate therapy for 6 months or longer is indicated by *in vitro* susceptibility testing (20). If it is pseudomonas and is sensitive to an aminoglycoside, and carbenicillin, then one would use combination therapy with an aminoglycoside with either carbenicillin or ticarcillin for 4-6 weeks, and thereafter retreat symptomatic recurrences.

TABLE 7

CORRELATION OF SINUS-TRACT CULTURES WITH OPERATIVE CULTURES (19)

Sinus Tract Isolates	No. of Patients	Consecutive Isolates (≥ 3) No. Agreeing with Operative Cultures	No. Disagreeing with Operative Cultures	Predictive Value, + %
Staphylococcus aureus	9	7	2	78
Enterobacteriaceae	8	5	3	62
Pseudomonas aeruginosa	6	-	6	0
Streptococcus sp	-	-	-	-
Total	23	12	11	52

V. Therapy of sexually transmitted diseases: Old diseases with a sexy new name, or why did a government committee have to change the name just because love is not always present?

A. Anorectal infection in a homosexual: The "Gay" bowel syndrome

RM is a 32 year old white male who noted the onset of bright red blood with bowel movements 2-3 days after a homosexual orgy in San Francisco. One week later, the patient began to pass blood eight to ten times a day in association with crampy, lower abdominal pain. He also noted tender swellings in both groin areas which diminished over the next week, leaving him with bilateral, firm, nontender nodes. At this time, his roommate also noted the onset of painful groin nodes without penile discharge or lesions which responded to tetracycline. RM had had no fever, chills, but he had begun to have night sweats at three weeks. The patient finally sought admission because of persistence after three weeks of the painful passage of blood per rectum and groin notes. On admission, he had bilateral hard, but nontender inguinal and femoral nodes without a prominent groove in the inguinal ligament. He had slight epigastric tenderness, but no left lower quadrant tenderness. Proctoscopic exam showed ulcerations at the anorectal junction with erythematous boggy mucosa for the first 5 cms. Multiple purulent erythematous lesions, approximately 2-3 mms in diameter, were noted up to 15 cms of the sigmoid colon, smears of the lesions showed moderate numbers of polymorphonuclear leukocytes with many gram-positive cocci but no extra- or intracellular gram-negative diplococci. Cultures from the lesions revealed heavy growth of Goup A β-hemolytic streptococcus and light growth of *Staphylococcus aureus*. Pharyngeal, urethral, and rectal culture were negative for *Neisseria gonorrhoea*. Laboratory tests were all within normal limits. VDRL was negative, stools for ova and parasites were negative X3, and amoeba titer was negative.

He was initially begun on tetracycline with a loading dose of 1½ gms po, followed by 500 mgs every 6 hours before meals. After the report of the culture he was given four days of cloxacillin 2 gms per day. On repeat proctoscopy after 8 days of tetracycline and 4 days of cloxacillin, the mucosa was only slightly erythematous but most of the lesions persisted without purulence; overall they appeared significantly improved. Repeat cultures

were negative. He was discharged to continue tetracycline for three weeks, but he failed to return for follow-up proctoscopy and convalescent LGV titers. An anti-hyaluronidase titer was 1:256, indicating recent streptococcal infection.

Patients presenting with proctitis should not only be questioned for a history of eating Jalapeno peppers or hot German sausage but also as to homosexual activity (71). Since a large number of etiological agents can produce rectal symptoms in the homosexual male, evaluation must consist of careful history, appropriate cultures and serological tests. In fact, in urban areas, venereal transmission in male homosexuals may account for the majority of cases of amebiasis, giardiasis, and shigellosis in those without travel history (72). The most commonly recognized infection in homosexuals is gonorrhea (73). Anorectal gonococcal infection is usually asymptomatic and is detected by doing cultures on homosexual men in VD clinics. Symptoms when present include painful defecation and occasional purulent discharge. Severe symptoms of proctitis as seen are very rare with anorectal gonococcal infections and rarely extend above 4 cm. Differential considerations in this case included amebiasis, shigellosis, syphilis, Herpes simplex II, lymphogranuloma venereum (LGV), chancroid, traumatic colitis, ulcerative colitis, ischemic colitis, or drug-induced (pseudomembranous) colitis. Workup as in this case should include proctoscopy with smears and cultures of involved muscosa (including darkfield examination), culture for gonococci on selective media, amoeba titer and VDRL and FTA.

Our presumptive clinical diagnosis in this case was LGV since this has been recognized as a cause of severe proctitis in females and males (74). Little credence was given to the possibility of streptococcal disease until the antibody test was returned. This organism was not present on first follow-up in spite of less than adequate therapy. Patients with LGV initially present with diarrhea, bloody and mucopurulent rectal discharge, followed by varying disturbances of defecation, tenesmus and even systemic evidence for infection. Mucosal involvement can be found from the anus up to 40 cms above the anus. Rectal stricture can develop months to years from onset of symptoms. The common-held belief that rectal stricture in females follows vaginal infection with secondary spread to lymph nodes is no longer tenable since lymphangitis alone could not explain mucosal involvement and microscopic evidence of proctitis was found in those who had rectal stricture (75). Diagnosis of LGV is made by four-fold rise in the psittacosis-LGV complement fixation test or suspected in anyone with a positive test greater than 1:32. LGV infections are usually responsive to tetracycline although treatment for 3 weeks and occasionally repeat courses may be necessary (76). Rectal stricture is a possibility following any LGV proctitis so close follow-up with repeat proctoscopy is required.

Treatment of other causes of proctitis depends upon correct recognition. Anorectal gonorrhea in men is not as responsive to usual treatment regimens as gonorrhea at other sites (73) (Table 8). Hence, extended therapy for anorectal disease has been tried: aqueous procaine penicillin (APPG) 4.8 million units IM followed by 2.4 million units APPG for 4 days or Spectinomycin 4 gm IM: both regimens achieving 100% cure rates in one trial (77). Cure rates for other gonococcal syndromes are also listed (78, 79). Recurrences of amebiasis do not necessarily indicate treatment failure but rather may represent reinfection in male homosexuals (80). Kean notes that the City of New York Department of Health had investigated the water supply in Greenwich Village two times before he came to "appreciate certain aspects of Greenwich Village life." (80).

TABLE 8

APPROPRIATE THERAPY FOR GONOCOCCAL INFECTIONS AT VARIOUS SITES

	Response Rate* %
Urethritis:	
Drug of Choice: aqueous procaine penicillin G (APPG), 4.8 million units I.M. with 1 gm probenecid	98
Alternative: Ampicillin 3.5 gm p.o. with 1 gm probenecid	95
Allergic to penicillin or probenecid: tetracycline 1.5 gm p.o. followed by 0.5 gm p.o. 4 times per day for 4 days	95
or	
Spectinomycin 2 gm I.M.	96
Anorectal Gonococcal (77):	
Drug of Choice: APPG, 4.8 million units I.M., followed by 2.4 million units daily for next 4 days	86/100
or	
Spectinomycin 4 gm I.M.	86/100
Pharyngeal:	
Drug of Choice: APPG. If failure to respond, tetracycline 1.5 gm p.o. followed by 0.5 gm p.o. 4 times a day for 4 days	80-90
Arthritis Dermatitis Syndrome (78, 79).	
Drug of Choice: aqueous crystalline penicillin G, 10 million units per day for 3 days (some continue ampicillin 2.0 gm p.o. per day for total of 10 days)	95+
or	
Ampicillin 3.5 gm p.o. with 1.0 gm probenecid, followed by ampicillin 2.0 gm per day p.o. for 7 days	95+
Allergic to Penicillin: erythromycin 500 mg IV every 6 hours for 3 days	†
or	
Tetracycline 1.5 gm p.o. followed by 500 mg 4 times a day for 7 days.	

*Response rates are dependent upon therapeutic compliance by patient. Failures may relate to failure to take drug. Hence, parenteral administration is recommended.
†Too few to be certain but no reported failures.

B. Nongonococcal urethritis, number 2 on the hit parade.

The patient with enterococcal endocarditis also presented with asymptomatic nongonococcal urethritis (NGU) as manifested by pyuria in an initially voided urine (1st 10 cc) without pyuria in a midstream urine. Since NGU is the second most common sexually transmitted disease, any young person with dysuria or pyuria should have an initial voided urine and a midstream (bladder) urine to determine if urethritis is present (81). Patients with an urethral discharge or with more than 4 polymorphonuclear leukocytes/HPF without intracellular gram-negative diplococci or urethral pyuria without bladder pyuria would be considered to have NGU (82). Up to 22% of asymptomatic sexually active polygamous men have NGU (82). Recent studies have shown that the two principal etiological agents in (NGU) are *Chlamydia trachomatis* and *Ureaplasma urealyticum*, previously known as T-strain mycoplasma (Table 9) (83). The isolation of *Chlamydia trachomatis* is made only in persons with NGU and was frequently associated with rise in antibody titer to the organism in this study. Although *Ureaplasma urealyticum* is isolated significantly more often from Chlamydia-negative patients with NGU than from Chlamydia-positive patients, it however is frequently isolated from uninfected individuals (83, 84). A positive association has been documented between isolation of this organism and sexual activity with more than 3 partners but clinical symptoms ensue under poorly understood circumstances (85). Rarely, Trichomonas is an etiological agent so it must be sought for and treated (82). Group B Streptococcus, *Hemophilus vaginalis* and other bacteria are not pathogenic since they are no more frequent in infected persons than in non-infected cases and in some cases are more common in uninfected cases (Table 9) (82, 83). The two principal causative organisms are also responsible for other clinical entities: *C. trachomatis* in pelvic inflammatory disease, epididymitis, ophthalmia neonatorum, a distinctive neonatal pneumonia, and *U. urealyticum* for perinatal mortality, low birth weight, infertility and puerperal sepsis (86, 87).

TABLE 9

FREQUENCY OF ISOLATION OF VARIOUS AGENTS IN PATIENTS WITH AND WITHOUT NGU (83)

	NGU			No NGU		
Agent	Present	Absent	# With Agent	Present	Absent	# Normal With Agent
Chlamydia	26	43	38	0	33	0
Ureaplasma urealyticum	46	23	67	23	16	59
Hemophilus vaginalis	3	66	4	19	14	58

Therapeutic trials have shown that tetracycline is effective in the treatment of NGU (84, 88). Sulfamethoxazole was effective for Chlamydia-positive NGU (92% response) whereas spectinomycin was not effective (7% cure rates) although this drug (spectinomycin) does achieve a cure in a majority of ureaplasma-positive cases (83). Holmes stated recently in Dallas that his preferred drug of choice was minocycline but this drug has not been established to be superior to tetracycline (84). Minocycline and doxycycline are more active in a tissue culture system (89). However, these drugs are more expensive than tetracycline; and significant vestibular side effects have been noted with minocycline, although the rate is higher in women (up to 30% of women treated with minocycline). Treatment for 7-10 days with tetracycline, 2 gm/day, is successful in 90% although relapses occur in up to 30% of patients. It has not been definitely established that treatment of the sex partners will decrease chances for relapse. This might be a formidable task if the epidemiologic information mentioned previously is true! Hence, repeated short course of tetracycline when symptoms recur are recommended (84).

C. Inguinal adenopathy: _____ _____ _____ _____

The differential diagnosis for inguinal adenopathy with penile lesions is shown in Table 10. If the patient has unilateral painless lymphadenopathy in association with a painless penile lesion, suspect syphilis and do a dark field examination of the ulcer or of aspirate from the lymph node (if no prior antibiotics). Infection with chancroid generally produces a painful, penile lesion and large painful unilateral inguinal lymph nodes. Infection with lymphogranuloma venereum (LGV) may be associated with transient penile lesions early in the course but no lesion is usually present when they present 3-4 weeks later with bilateral large adenopathy (Bubo) which is only mildly tender (74). If both inguinal and femoral nodes are large, a "groove" sign develops due to accentuation of the inguinal ligament. Granuloma inguinale and herpes simplex virus type 2 rarely present with lymphadenopathy but with penile lesions alone. In fact, granuloma inguinale is seen predominantly in homosexual men as perianal or penile beefy-red granulation tissue with indurated swelling, occasionally extending to inguinal area (90). Syphilis frequently coexists with granuloma inguinale. Obviously the differential diagnosis of lymphadenopathy without penile lesions would include skin infections of the lower extremity, cat scratch fever, and lymphoma. Since it may be difficult to determine the etiology of inguinal adenopathy in association with penile lesions, individuals in whom a diagnosis can not be established after careful clinical examination should be treated with tetracycline for 10 days since this drug is adequate treatment for syphilis and is the treatment of choice for LGV and chancroid. In a recent epidemic of chancroid in Canada, an occasional tetracycline-resistant strain was isolated for which case sulfisoxazole or kanamycin may be used (91).

TABLE 10

DIFFERENTIAL DIAGNOSIS OF PENILE LESIONS WITH INGUINAL ADENOPATHY

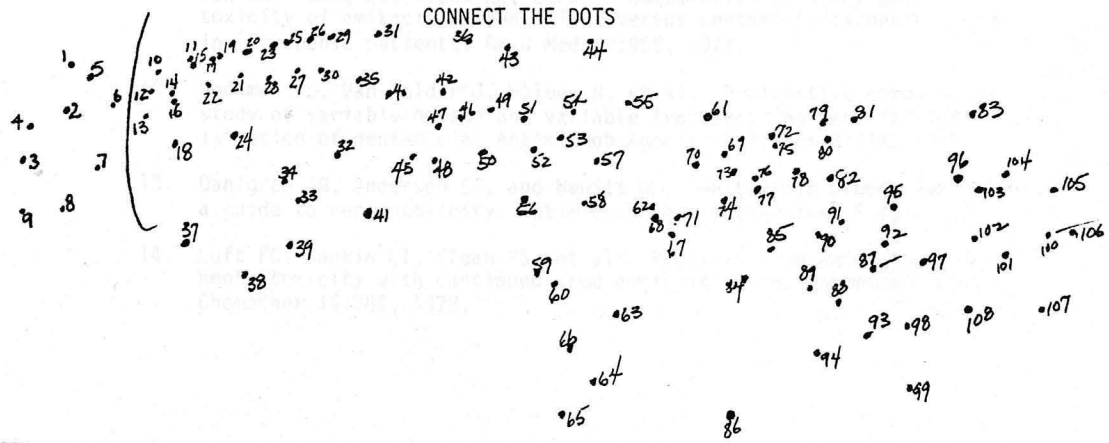
	Penile Lesion	Lymphadenopathy
Syphilis	Present, painless	Unilateral, painless
Chancroid	Present, painful	Unilateral, painful
LGV	History ±	Large, bilateral or unilateral
Granuloma Inguinale	Present	Absent
Herpes Simplex II	Present	Absent

ACKNOWLEDGEMENTS:

I wish to acknowledge: the masterful handling of case #1 by R. Farkas and W. Maddox; the many houseofficers who patiently administered to GM., I. Pike and W. Maddox for care of J.C. and L.C., review of literature by D. Fort and R. White, careful GI evaluations by R. Hendler, G. Willeford and I. Seeman, and the perceptive inquiries of many house-officers. I also appreciate the hard work and patience of P. Shirley and P. Brooks.

TABLE 11

CONNECT THE DOTS



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