USE OF ANTIBIOTICS IN THE ELDERLY*

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CHEMOTHERAPEUTIC drugs utilized in the treatment of infectious diseases interact with both infectious agents and the human host. This discussion will emphasize the latter relation, especially with regard to care of the elderly.

DRUG USE IN THE ELDERLY

This subject has been reviewed by Vestal[1] and summarized in Table I. In fiscal year 1976 the aged spent about 25% of the national total of 11.2 billion dollars for drugs. Expenditures for drugs by the elderly in the United States may constitute more than 40% of the national total by the year 2030. It is clear that the needs of geriatric patients constitute an increasingly important aspect of medical care for the future. Although not unique to geriatric medicine, medication errors and lack of comprehension are prevalent and undoubtedly contribute to the increased incidence of adverse drug reactions among the elderly. A study of 714 hospitalized patients at the Johns Hopkins Hospital revealed that 24% of patients over the age of 80 had adverse drug reactions compared with 11.8% in patients 41 to 50 years old.

It is believed that older patients are more susceptible to both the therapeutic and toxic effects of many drugs. Some pharmacokinetic age differences have been documented and tend to be consistent with age-related changes in body composition, protein binding, hepatic drug metabolism, and renal excretion. Body composition is an important determinant of any distribution and differs with age, characterized by 10 to 15% reduction of

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TABLE I. DRUG USE IN THE ELDERLY

A. Epidemiology—medication errors and lack of comprehension contribute to adverse drug reactions.

B. Altered physiology

1. Decrease in lean body mass and total body water
2. Decrease in serum albumin concentration
3. Decline in renal glomerular and tubular function
4. Diminished cardiac output, hepatic and cerebral blood flow.

Hepatic microsomal enzyme activity influenced more by biologic variation than age

Little effect of age on drug absorption has been documented.

C. Increased sensitivity to drugs—including therapeutic and toxic effects.

TABLE II. PLASMA PROTEIN BINDING

Agent	%	*Agent*	%
Antifungal drugs			
Amphotericin B	90	Cephradine	10
5-Fluorocytosine	<10	Cefamandole	75
Antituberculous drugs		Cefoxitin	65
Isoniazid	<10	Penicillins	
Rifampin	60 to 90	Penicillin G	20 to 60
Ethambutol	<10	Ampicillin	16 to 20
Aminoglycosides	0 to 20	Methicillin	37
Cephalosporins		Dicloxacillin	96
Cephalothin	65	Oxacillin	92
Cephapirin	45	Carbenicillin	50
Cefazolin	80	Ticarcillin	45

TABLE III. DECREASED ALBUMIN BINDING OF ANTIMICROBIALS

1. Increases tissue distribution
2. Increases penetration into interstitial space
3. Increases glomerular filtration (cefazolin) but no effect on tubular secretion (methicillin, oxacillin, cloxacillin)
4. Effect on hepatic metabolism and biliary excretion not clear
5. Increased free drug for antimicrobial activity

body water, decrease of lean body mass, and increased body fat. Standard drug doses might be expected to result in higher blood and tissue levels.

Serum albumin is reduced in old age. One study compared serum protein concentrations in 50 young normal adults with 90 elderly subjects ranging in age from 65 to 103 years.[2] Total serum protein levels were

similar, but young subjects had a mean albumin concentration of 4.7g./dl. compared to 3.8g./dl. in the elderly subjects who also had increased globulin levels. A disturbance of the normal metabolic response to the stimulus of a reduced albumin pool seems to be present in some elderly individuals. Decreased quantities of serum albumin should provide more free drug for diffusion into body tissues. There are several binding sites on each albumin molecule, and the extent of binding varies from practically zero with cephaloridine, kanamycin, vancomycin, polymyxin B, colistin, and isoniazid to more than 90% for oxacillin, cloxacillin, dicloxacillin, novobiocin, demeclocycline, sulfadimethoxine, and sulfamethoxypyridazine (Table II). Chemotherapeutic agents with high plasma binding are expected to provide more free drug in elderly subjects with reduced serum albumin. The marked variation in binding with the penicillins and cephalosporins occurs because the aromatic side chain is primarily involved in binding. Reduced serum protein binding of antimicrobial agents should increase tissue distribution, penetration into interstitial spaces and inflammatory fluids, elimination, and biologic activity (Table III).[3]

Removal of drugs from the body by liver metabolism and renal excretion may be altered in the elderly. Some evidence suggests that in man the aging process may alter the intrinsic metabolic capacity of the liver, but studies with antipyrine indicate that inter-individual variation exceeds the effect of age. A recent study[4] comparing the effects of age in the oxidation of acetanilide and the acetylation of isoniazid found a significant prolongation of the plasma half-life of acetanilide in the elderly subjects but no age difference with isoniazid, indicating that nonmicrosomal enzyme pathways may be unaffected by age.

Aging appears to affect both glomerular and tubular function. Glomerular filtration rate falls an average of 35% between ages 20 and 90. Renal plasma flow declines approximately 1.9% per year. In the young, the glomerular filtration rate falls to about 30 ml./minute before elevation of serum creatinine while in older patients with reduced body mass, the glomerular filtration rate must fall to a lower value before serum creatinine levels rise. Thus diminished renal function is common among the elderly and is an important aspect of the use of antimicrobials.

Renal Insufficiency

Drugs handled predominantly by the liver must be administered in full therapeutic doses to patients with renal insufficiency to provide therapeu-

TABLE IV. HEPATOBILIARY EXCRETION OF ANTIMICROBIAL AGENTS

Nafcillin	Lincomycin	Chloramphenicol
Ampicillin	Chlorlincomycin	Isoniazid
Aureomycin	Erythromycin	Rifampin

tically equivalent serum levels. Some of these antimicrobial agents are listed in Table IV. However, dosage should be reduced in the presence of hepatic insufficiency. The role of hepatic dysfunction in the pathogenesis of toxic reactions to chloramphenicol was determined by Suhrland and Weisberger[5] in 16 patients with decreased liver function who were given a dose of 500 mg. orally four times a day for one month or until toxicity was detected. Fifty percent of the patients with cirrhosis and 6 of 19 with renal disease manifested depression of erythropoiesis which was demonstrated in none of the normal subjects.

Penicillin is cleared by glomerular filtration (10%) and tubular excretion (90%). The half-life is 30 minutes in normal patients and increased to between seven and 10 hours in the presence of anuria. If, in addition to renal insufficiency, hepatic dysfunction is present, the antibiotic may persist in the blood for as long as 16 to 30 hours. A loading dose followed by additional injections every eight to 16 hours has been recommended when renal shutdown is present. Doses of ampicillin and beta-lactamase resistant penicillins do not require marked alteration, although half-lives may be prolonged. Because half-lives of carbenicillin and ticarcillin approximate two hours in the normal and are markedly prolonged with anuria, changes in dosage are necessary, especially if hepatic dysfunction coexists. Less is known about azlocillin, mezlocillin, and piperacillin, but their pharmacology appears to resemble that of ampicillin, and marked dosage adjustment is not required until the creatinine clearance falls below 30 ml./min. All cephalosporins except cephazolin are rapidly excreted by the kidneys and hence have relatively short half-lives, similar to the penicillins, so that half-life prolongation secondary to renal insufficiency requires only modest dosage alteration.

Because aminoglycosides have a relatively low therapeutic index (therapeutic/toxic serum level), dosage adjustments for renal function are necessary (Table V). In normal individuals, the first-phase half-life approximates two hours while the terminal elimination phase following accumulation in renal cortical tissue averages 160 hours. In patients with

TABLE V. THERAPEUTIC AND TOXIC LEVELS OF AMINOGLYCOSIDES

	Trough level (μg/ml.)	*Peak level (μg./ml.)*	
		Therapeutic	*Toxic*
Gentamicin, tobramycin, netilmicin	0-2	4-8	>12
Amikacin	0-5	5-25	>35

Calculated creatinine clearance, ml./min., for use with the variable dosage regimen aminoglycoside administration

$$\text{Clearance cr} = \frac{(140\text{-age}) \times \text{weight in Kg.}}{\text{Serum conc. cr} \times 72}$$

normal renal function, an initial dose of gentamicin, tobramycin, or netilmicin of 1.5 mg./kg. of body weight followed by 1.5 mg./kg. every eight hours will produce adequate serum levels. A dose of 5 mg./kg. of amikacin every eight hours will provide adequate levels.

Dosage adjustment in the presence of decreased renal function may be based on modification of frequency or administered amount. With the initial method, 1.5 mg./kg. of gentamicin and 7.5 mg./kg. of amikacin is given every eight hours times the serum creatinine in mg./dl. With the latter method, a loading dose of aminoglycoside is given (1.5 mg./kg. gentamicin or 7.5 mg./kg. amikacin) followed by a percent of the dose administered every eight hours based on the calculated creatinine clearance. The percentage of dose to be administered can be calculated from regression lines available for each drug.[6,7] The second method should provide higher serum levels and reduce the risk of breakthrough bacteremia.

MONITORING TREATMENT BY SERUM ASSAY

Measurement of serum levels of toxic antimicrobial agents is a valuable clinical aid. Several methods are listed in Table VI.

Agar disk diffusion bioassay. Concentrations of antibiotic (1.5, 6, and 12 μg./ml.) for a standard curve and the patient's serum are impregnated in sterile filter paper disks. If the patient is receiving a combined antimicrobial regimen of an aminoglycoside and a penicillin or cephalosporin, the serum must be pretreated with penicillinase (cephalosporinase) prior to

TABLE VI. ASSAYS FOR ANTIMICROBIAL AGENTS

Specific	1. Agar disk diffusion	Serassay
	2. Agar well diffusion	
	3. Automated radiometric	SAG, SAT, SAA
	4. Radioimmunoassay	
	5. High pressure liquid chromatography	
Nonspecific	1. Schlichter test	MBC MIC

testing. The disks are placed on the surface of an agar plate previously seeded with *Bacillus subtilis* susceptible to the aminoglycoside. After incubation for four to five hours, the zone of inhibition around each antibiotic disk is measured to the nearest millimeter and used to plot a standard curve with the zone diameter on the ordinate and the concentration of the aminoglycoside antibiotic on the abscissa. The concentration of antibiotic in the patient's serum is extrapolated from the standard curve using the diameter of the zone of inhibition. The results are clinically adequate, but the procedure is time consuming and tedious. The zone of inhibition is influenced by several variables, including the freshness of the plate and the level of the agar surface. Commercial test reagents are available for gentamicin, tobramycin, and amikacin. The method has also been utilized to quantify serum levels of vancomycin, clindamycin, chloramphenicol, tetracycline, and metronidazole.

Agar well diffusion bioassay. This modification of the disk-diffusion method utilizes a strain of *S. epidermidis,* resistant to almost all antibiotics except aminoglycosides, and circumvents the problem of neutralizing other antibiotics.

Automated radiometric bioassay. Urea induces the synthesis of urease in a species of *Proteus* which is inhibited by gentamicin. With inhibited urease synthesis, less urea will be metabolized to CO_2 and ammonia. The Bactec-SAG (Johnston Laboratories, Inc., Cockeyville, Md.) uses this principle to measure the level of gentamicin in a patient's serum by comparing the amount of CO_2 released in bottles containing patient's serum to the amount of CO_2 released in bottles containing known amounts of gentamicin, ^{14}C-labelled urea is metabolized to $^{14}CO_2$ and ammonia by the urease synthesized by *Proteus*. The same principle applies to tobramycin and amphotericin B assays. Advantages are clear and include rapid reporting (within one hour), neutralization of other antibiotics is not neces-

sary, and automation eases performance. The principal limitation is the requirement for Bactec instrumentation, which can also be used for detection of bacteremia and *Neisseria* identification.

Radioimmunoassay of aminoglycosides. Radioimmunoassay is used to measure circulating levels of amikacin, gentamicin, and tobramycin with commercially available reagents. Recently developed RIA-amikacin and gentamicin kits do not require preliminary sample extraction. The assay consists of competitive binding of serum and ^{125}I-labelled amikacin to specific antibody, separation of free from bound amikacin with goat antirabbit gamma globulin and counting the antibody-bound ^{125}I-labelled amikacin in a suitable gamma counter. There is no cross-reactivity with most of the structurally related aminoglycosides or other antimicrobials commonly encountered in the serum of patients being treated with amikacin.

Other assay methods. High-pressure liquid chromatography has been studied extensively and is capable of reliably detecting chloramphenicol, 5-fluorocytosine, metronidazole, netilmicin, gentamicin, cefazolin, amphotericin B, and tetracycline. Enzymatic adenylylation and acetylation has been utilized to monitor gentamicin, sisomicin, kanamycin, tobramycin, amikacin, and chloramphenicol while release of radiolabelled rubidium is reported for determination of amphotericin B.

The nonspecific serum Schlichter assay may be useful in evaluating therapy. This test utilizes twofold dilutions of serum to which are added a constant volume of an overnight culture of the isolate from the patient. After overnight incubation at 35°C., the clear tube with the highest serum dilution is taken as the bacteriostatic titer. Subculture of clear tubes is required to determine the bactericidal serum titer. A serum bactericidal titer of 1:8 or greater is regarded as desirable for treatment of endocarditis. Klastersky et al.[8] have utilized the serum and urine inhibitory level to predict response to antimicrobial therapy in 317 patients with cancer and bacteriologically proved infection. When the peak titer of bacteriostatic activity in serum was ≥1:8, the infection was cured in more than 80% of cases. The response to therapy of patients with urinary tract infections correlated best with the inhibitory level found in the urine. Clinical cure was observed in at least 90% of the patients who had a titer of bacteriostatic activity in urine ≥1:4. The advantage of this monitoring method is that it can be performed by most laboratories and avoids cumbersome synergy assays which are not readily available.

TABLE VII. COMBINATION ANTIMICROBIAL THERAPY IN GRANULOCYTOPENIA

	Response rate		*Nephrotoxicity*	
EORTC[9]—625 trials				
Carbenicillin + cephalothin	>70%		4%	
Carbenicillin + gentamicin	>70%		2%	
Cephalothin + gentamicin	>70%		12%	
Carbenicillin + amikacin	>75%			
Wade et al.[10]—135 patients				
Cephalothin + gentamicin			30.4%	25.5%
Cephalothin + tobramycin			20.8%	
Methicillin + gentamicin			10%	7%
Methicillin + tobramycin			4.3%	
Baltimore Cancer Group—Love et al.[11]				
	Overall	*Bacteremia*		
Ticarcillin + gentamicin	97%	93%	2%	
Ticarcillin + amikacin	91%	78%	6%	
Ticarcillin + netilmicin	95%	82%	2%	

TABLE VIII. ALLERGIC AND TOXIC REACTIONS TO DRUGS USED IN GRANULOCYTOPENIC PATIENTS

A. Carbenicillin/ticarcillin
- Hypersensitivity
  - IgE— anaphylaxis urticaria
  - IgG— hemolytic anemia, neutropenia, interstitial nephritis, vasculitis
- Hepatitis
- Seizures
- Hypokalemic alkalosis (due to anion load)
- Sodium retention (30 gm. contains 150 meq. Na^+)
- Impair platelet function (block platelet receptors)
- Hyperstenuria

B. Cephalothin/cephapirin
- Hypersensitivity—same as above
- False-positive direct Coombs test
- Hepatitis
- Seizures
- Nephrotoxicity in synergy with aminoglycosides

C. Aminoglycosides
- Ototoxicity—2 to 10%
- Nephrotoxicity—2 to 25%
- Neuromuscular blockade
- Neutropenia

TABLE IX. PENICILLIN SKIN TEST REAGENTS

Antigen	*Highest concentration*
Aqueous penicillin G	10,000 μ./ml.
Penicilloyl polylysine	6×10^{-5}M/ml.
Benzyl penicilloate	1×10^{-2}M/ml.

TOXICITY OF MULTIPLE ANTIMICROBIAL AGENT THERAPY

In immunosuppressed patients with neutropenia, approximately 60% of episodes of fever can ultimately be associated with bacteria. Rapid institution of antibiotic programs improves their prognosis. Until recently, combination therapy with carbenicillin (5 gm. q. 4h.) gentamicin and cephalothin/cephapirin (2 gm. q. 4h.) has been utilized. Large prospective comparative trials suggest that three-drug combination therapy may not be necessary (Table VII).[9-11] In fact, cephalosporins appear to induce increased nephrotoxicity when compared to carbenicillin/ticarcillin combinations with aminoglycosides. A combination of carbenicillin or ticarcillin with an aminoglycoside appears to have the best ratio of efficacy to toxicity for initial empiric therapy of infection in granulocytopenic patients with cancer. It is logical to continue treatment for a total of five days without fever if the cultures are not positive and for 10 days if an organism is isolated. Antibiotics should not be continued more than one week in a persistently positive febrile patient without positive blood cultures. These recommendations are based on the observation that superinfection increases after seven days of therapy if an organism is not isolated.

Allergic and toxic manifestations of drugs commonly used in granulocytopenic patients are listed in Table VIII. Evaluation of penicillin hypersensitivity involves skin testing intradermally with serial dilutions up to 10,000 K/ml. penicillin G, 6×10^{-5} M/ml. penicilloyl polylysine and 1×10^{-2} M/ml. sodium penicilloate (Table IX). The last antigen is not available commercially but can be prepared as follows:

Aseptically introduce 8.5 ml. of sterile 0.1N NaOH and 1.5 ml. of sterile physiological saline into a vial of potassium penicillin G, one million units (Squibb). Swirl the vial to complete solution and incubate 45 minutes at room temperature (70-75°F.) and 48 hours in the refrigerator.

TABLE X. INTERACTION OF ANTIBIOTICS WITH HOST DEFENSES

Inhibition of chemotaxis —	Tetracycline Rifampin Fusidic acid Amphotericin B Chloramphenicol
Depression of cell-mediated immunity	5-Fluorocytosine ? Amphotericin B Rifampin Fusidic acid ? Cephalosporins ? Cephamycins Chloramphenicol
Antibody production	Chloramphenicol

The stock solution is stable for one month under refrigeration. Dilute 0.8 ml. of this benzylpenicilloate stock solution in 9.2 ml. sterile physiological saline. Prepare fresh each day and keep refrigerated.

EFFECT OF ANTIMICROBIALS UPON HOST CELLULAR DEFENSES

Although the primary concern has been with the interaction of antibiotics upon infectious agents, recent studies indicate effects upon the host which may play a role in compromising defense mechanisms. Some of the observed effects are summarized in Table X.

INTERACTION AMONG ANTIBIOTICS AND OTHER DRUGS

The problem of drug interactions is complicated both by lack of knowledge and by the physician's difficulty in being aware of those that are clinically relevant. The mechanisms involved include displacement from carrier sites, competition for renal tubular secretion, interactions controlled by hepatic enzymes, interactions at tissue sites, and interactions controlled by pH. In elderly patients characterized by hypoalbuminemia, displacement from serum carrier sites is especially important.[12]

PREVENTIVE THERAPY IN COMPROMISED HOSTS

Several modalities of therapy have been utilized in the therapy of leukopenic patients. These are summarized in Table XI and have been

TABLE XI. PREVENTIVE THERAPY IN THE COMPROMISED HOST

Protective environment
Oral nonabsorbable antibiotics
Gentamicin 200 mg. q. 4 h.
Vancomycin 250 mg. q. 4 h. (optional)
Mycostatin 20,000,000 units daily
Granulocyte transfusions
Trimethoprim—sulfamethoxazole (TMP-SMZ)
(320 mg.) (1,600 mg.)

surrounded by controversy. The most promising new development has been the use of trimethoprim and sulfamethoxazole. Hughes et al.[13] reported that 17 of 80 patients receiving a placebo acquired *Pneumocystis carinii* pneumonitis, whereas none of the 80 given 150 mg. of trimethoprin and 750 mg. of sulfamethoxazole per square meter per day acquired the infection. Other bacterial infections also occurred less frequently in recipients of the drug. In another study,[14] hospitalized granulocytopenic patients were allocated at random to receive this therapy or to a control group. The favorable results suggest that oral prophylactic trimethoprim and sulfamethoxazole therapy is an effective, well-tolerated, easily administered alternative to nonabsorbable antibiotics.

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