Manual of Antibiotics and Infectious Diseases

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Fourth Edition

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Fourth Edition

LEA & FEBIGER Philadelphia • 1981

Lea & Febiger
600 Washington Square
Philadelphia, PA 19106
U.S.A.

Library of Congress Cataloging in Publication Data

Conte, John E
Manual of antibiotics and infectious diseases.

Bibliography: p.
1. Antibiotics. 2. Communicable diseases—Chemotherapy. I. Barriere, Steven L., joint author. II. Title. [DNLM: 1. Antibiotics—Handbooks. 2. Communicable diseases—Drug therapy—Handbooks. QV 350 C761m]
RM267.C63 1981 616.9'0461 81-442
ISBN 0-8121-0768-3 AACR1

Published in Great Britain by Henry Kimpton Publishers, London

PRINTED IN THE UNITED STATES OF AMERICA

Print No. 3 2 1

Preface

This manual is designed for students, housestaff, practicing physicians, and other health professionals involved in the day-to-day care of patients with infectious diseases. An attempt has been made to incorporate into 1 book a variety of important source materials that ordinarily can be found in many different locations.

The manual is divided into 9 sections:

Section I. Antibiotics

Clinically important information is presented for each antibiotic. In some instances, 2 or 3 antibiotics that are similar are discussed together. This section includes the availability and trade names of each drug, its clinical use, administration and dosage, dosage in renal insufficiency, pharmacology, adverse reactions, and drug interactions. Further reading lists are also supplied.

Section II. Pharmacokinetic Principles

Basic principles of the handling of drugs by the body are provided, with simple formulas for estimating half-life in renal insufficiency and calculating a dosage regimen for the individual patient. Recommendations are also provided for the determination of antibiotic blood levels and serum antimicrobial activity.

Section III. Empiric Antibiotic Therapy

Recommendations are made for drugs of choice, alternative therapy, appropriate dosages, and routes of administration for various clinical situations in which infection is suspected.

Section IV. Therapy of Established Infection

Empiric antibiotic therapy is continued until gram stains and cultures from the laboratory reveal 1 or more specific agents. At this point, specific therapy is begun; this section summarizes antibiotic choices, doses, route of administration, and duration of therapy

Section V. Antibiotic Sensitivities

Section VI. Prophylactic Antibiotics

This section provides guidelines for the use of prophylactic antibiotics; general principles; American Heart Association recommendations for the prevention of endocarditis during various surgical procedures; American Heart Association recommendations for the prevention of rheumatic fever; tuberculosis; malaria; and meningococcal infection.

Section VII. Availability and Clinical Use of Immunobiologic Agents and Antiparasitic Drugs

These agents are available by request from the Immunobiologics, Biologic Products Division, Bureau of Laboratories, of the Center for Disease Control. Guidelines are given for the use of BCG; immune serum globulin and hepatitis B immune globulin; influenza vaccine; pneumococcal vaccine; polio vaccine; rabies immune globulin and duck embryo vaccine; zoster immune plasma; tetanus prophylaxis; immunobiologic agents and drugs distributed by the CDC and drugs for the treatment of parasitic infections.

Section VIII. Viral Hepatitis: Clinical and Serological Summary

This section includes hepatitis nomenclature; clinical comparison of Hepatitis A, B, and non-A and non-B; serologic markers and tests for hepatitis; and incidence of Hepatitis B markers in various populations.

Section IX. Syphilis and Gonorrhea

United States Public Health Service recommendations for the treatment of syphilis and gonorrhea are provided.

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Abbreviations

bid	twice a day
BUN	blood urea nitrogen
cc	cubic centimeter
CDC	Center for Disease Control
CNS	central nervous system
Cl_{CR}	creatinine clearance
C_P	plasma concentration
Cr_S	serum creatinine
CSF	cerebrospinal fluid
dl	deciliter(s)
F	availability (per cent oral absorption expressed as a fraction)
FTA-ABS	fluorescent treponemal antibody absorption (test)
GI	gastrointestinal
g.	gram(s)
G6PD	glucose-6-phosphate dehydrogenase (deficiency)
hr	hour(s)
ID	intradermal
IM	intramuscular
IT	intrathecal
IU	international unit(s)
IV	intravenous
kd	elimination rate constant
KF	kidney function
kg	kilogram(s)
L	Liter
LD	loading dose
LP	lumbar puncture
M	molar
MBC	minimum bactericidal concentration
mcg	microgram(s)
MD	maintenance dose
meq	milliequivalent
mg	milligram(s)
MIC	minimum inhibitory concentration
MLC	minimum lethal concentration
ml	milliliter(s)

MU	million units
PO	by mouth
PPD	purified protein derivative (of tuberculin)
qd	daily, once a day
qid	4 times a day
qod	every other day
q2h	every 2 hours
q4h	every 4 hours
q6h	every 6 hours
q8h	every 8 hours
q12h	every 12 hours
RBC	red blood cell
RPR	rapid protein reagin
SIADH	syndrome of inappropriate antidiuretic hormone secretion
T	dosing interval
$t_{1/2}$	half-life
TB	tuberculosis
tid	3 times a day
U	unit(s)
UTI	urinary tract infection
V_d	volume of distribution
VDRL	Venereal Disease Research Laboratories

Contents

Section I

ANTIBIOTICS

The summaries of antibiotics that follow are designed to provide the clinician with an overview of the clinical use of each agent, along with pertinent facts concerning comparative efficacy and toxicity, if similar agents are available. Each section provides information on appropriate dosage and administration in patients with normal and impaired renal function and other important clinical pharmacologic parameters. Sections on adverse reactions and significant drug interactions are provided, and finally, a few references are listed to allow the reader to review each agent in more depth or to investigate more controversial points.

An attempt is made to provide information on all currently useful antibiotics. Older drugs that have fallen into relative disuse are not included. For example, semisynthetic penicillins such as phenethicillin or hetacillin, cephalosporins such as cephaloridine or cephaloglycin, aminoglycosides such as neomycin, or agents such as triacetyloleandomycin have little to no role in current clinical medicine and are either less effective or more toxic than new agents. Recent clinical data suggest that tobramycin is the least nephrotoxic aminoglycoside currently available, and the recommendations contained in the manual reflect this finding. Our experience and other clinical data document the relative lack of interstitial nephritis secondary to nafcillin. Since methicillin is associated with a significant incidence of nephritis, and since oxacillin is hepatotoxic, recommendations in the manual are for the use of nafcillin in the treatment of staphylococcal infection.

Several tetracycline and sulfonamide derivatives are deliberately excluded, since these analogs offer no advantage over tetracycline or sulfisoxazole in the treatment of infectious diseases. Exceptions to this are noted in the summaries of each drug. It must be emphasized that although the summaries reflect the majority of opinions on clinical use, they also contain our opinions and interpretation of the available data, as well as our experiences.

At the time of this writing, several semisynthetic penicillins and cephalosporins are being tested in clinical trials. A few of these agents

may shortly become commercially available. They all possess enhanced activity against many gram-negative bacilli, notably *Serratia marcescens* and *Pseudomonas aeruginosa.* Penicillin derivatives such as piperacillin, azlocillin, and mezlocillin and cephalosporins such as cefoperazone and cefotaxime hold promise for the treatment of serious gram-negative bacillary infection, without the potential for nephro- or ototoxicity.

Other agents that will soon be available and may be useful in selected situations include: cefuroxime, a cephalosporin active against the gonococcus, including penicillinase-producing strains (PPNG); trimethoprim as a sole agent, which may be useful in those patients with recurrent UTI who cannot tolerate a sulfonamide; and netilmicin, an aminoglycoside, active against many gentamicin- or tobramycin-resistant gram-negative bacilli, that may be less toxic than gentamicin.

AMANTADINE

This drug is available as a red capsule containing 100 mg and as a syrup containing 10 mg/ml.

Clinical Use. Amantadine, a synthetic antiviral agent, inhibits RNA viral replication and prevents the penetration of virus into susceptible cells. It is only active against strains of influenza A virus. The drug is ineffective against influenza B. Clinical use of amantadine is suggested in the following:

a. household contacts
b. prevention of institutional spread } prophylaxis
c. unvaccinated adults at high risk
d. treatment of acute infection within 48 hours of onset of illness, in an attempt to lessen symptomatology

Administration and Dosage. Adults and older children: 100 mg (1 capsule or 10 ml of syrup) PO bid, for treatment or prophylaxis. Younger children (<10 years old): 3 mg/kg/day. Since the drug is effective for prophylaxis during the period of administration only, it should be given for 10 days after exposure to a single case and up to as long as 4 to 6 weeks with repeated exposure during an epidemic.

Dosage in Renal Insufficiency. The drug is nearly entirely excreted unchanged, so dosage should be reduced in proportion to the decrease in creatinine clearance. Hemodialysis has little effect on clearance.

No data are available regarding peritoneal dialysis.

Pharmacology. Serum concentrations have not been correlated with therapeutic effect. The serum half-life is approximately 12 hours in patients with normal renal function. Excretion is enhanced by acidification of the urine.

Adverse Reactions

CNS Toxicity. Nervousness, dizziness, agitation or ataxia, drowsiness, and insomnia may result.

Anticholinergic Reactions. Blurred vision, dry mouth, and tachycardia may occur.

Gastrointestinal Disturbance. Anorexia and nausea are mild.

Teratogenic Reactions. None are reported.

Drug Interactions. None are known.

Further Reading

Monto, A.S., et al.: Prevention of Russian influenza by amantadine. J.A.M.A., *241*:1003, 1979.

AMIKACIN

This drug is available as solution for injection in vials containing 500 mg/2 ml, 1000 mg/4 ml, and 100 mg/2 ml for pediatric use. (Amikin)

Clinical Use. Amikacin is a semisynthetic aminoglycoside active against nearly all gram-negative bacilli, including many strains resistant to gentamicin or tobramycin. Amikacin is bactericidal and inhibits protein synthesis by binding to the 30s subunit of bacterial ribosomes. Many institutions, including our own, have restricted its use to infections caused by resistant organisms. The effects of this restricted use on the emergence of resistance to amikacin is unknown. It is clinically useful in a variety of infections due to susceptible pathogens, including infections of bones and joints, the respiratory tract, soft tissue and wounds, the urinary tract, and the central nervous system, as well as septicemia.

Administration and Dosage. Adults and children: 15 to 20 mg/kg/day IM/IV, in 2 or 3 divided doses. Neonates and infants: maximum of 15 mg/kg/day IM/IV. Older children may receive 20 to 30 mg/kg/day IM/IV. The dose is diluted into 100 to 200 ml of a compatible IV solution and is infused over 30 to 60 minutes. Intrathecal or intraventricular dosage for meningitis is 10 to 15 mg per day.

Dosage in Renal Insufficiency. One should consult the nomogram (see Table II–2) for adjusting aminoglycoside dosage or refer to the section on pharmacokinetic principles to estimate half-life. A loading dose should always be administered to achieve adequate serum levels. Subsequent doses may then be reduced, based on the patient's renal function. The half-life of amikacin during hemodialysis is approximately 4 hours. Peritoneal dialysis has little effect on the drug's half-life.

Pharmacology

	Dosage mg/kg IV	Serum Concentration (mcg/ml)	Urinary Concentration (mcg/ml)	V_D L/kg	Normal $t_{1/2}$ (hr)	Anuria $t_{1/2}$ (hr)	Protein Bound (%)	Excreted Unchanged (%)
Adult	7.5	20–30	500–1000	0.25–0.3	2	≥48	Low	90–95
Neonate	7.5	15–20	500–1000	0.5–0.6	5–7	≥48	Low	90–95
Child	7.5	20–25	500–1000	0.3	1.5	≥48	Low	90–95

CSF penetration: variable; maximum of 40 to 50% of serum levels, but IT administration is required. Pleural and ascitic fluid levels are nearly equal to serum levels.

Adverse Reactions

Ototoxicity. High-frequency hearing loss and tinnitus occur after prolonged (>10 to 14 days) therapy. Hearing loss in the conversational range and vestibular damage are rare, but may be irreversible.

Nephrotoxicity. Acute tubular necrosis occurs in 5 to 10% of patients and is manifested by increases in serum creatinine and BUN.

Neuromuscular Blockade. This has only been reported with kanamycin or neomycin, administered by intraperitoneal lavage, and in patients given full IV dosage in the presence of renal insufficiency.

Drug Interactions

Cephalosporins. The potential for synergistic nephrotoxicity exists, although this is controversial and has only been documented for gentamicin and tobramycin.

Potent Diuretics (furosemide, ethacrynic acid). These are felt to potentiate oto- or nephrotoxicity presumably due to volume contraction.

Penicillins. Inactivation of the aminoglycosides is caused *in vitro* and *in vivo.* Caution should be exercised in patients with renal insufficiency, in whom excessive concentrations of penicillins may result in decreased aminoglycoside concentrations. Amikacin is inactivated to a lesser extent than the other agents. The clinical significance of this interaction is unknown.

Miscellaneous. Aminoglycosides may enhance the nephrotoxicity of platinum compounds, amphotericin B, and polymyxins.

Further Reading

Finland, M., et al.: Advances in aminoglycoside therapy—amikacin. J. Infect. Dis. [Suppl.], *134*:51, 1976.

Hewitt, W.L., et al.: U.S. amikacin symposium. Am. J. Med., *62*:1, 1977.

AMOXICILLIN

This drug is available in capsules containing 250 mg and 500 mg and in oral suspensions containing 125 mg/5 ml and 250 mg/5 ml. (Larotid, Amoxil, and others)

Clinical Use. Amoxicillin is a semisynthetic analog of ampicillin. Except for shigella, its *in vitro* activity is similar to that of ampicillin (see ampicillin for spectrum and mechanism of action). It is clinically useful in urinary tract infections, upper and lower respiratory tract infections, skin and soft-tissue infections, and gonorrhea. An advantage of amoxicillin over oral ampicillin is more reliable absorption, resulting in serum levels that are approximately twice as high. Amoxicillin may be

useful in the chronic treatment of endocarditis or osteomyelitis, if compliance and adequate serum bactericidal activity can be assured.

Administration and Dosage. Adults and children: 25 to 100 mg/kg/day, in 3 or 4 divided doses, depending on the severity and the site of infection.

Dosage in Renal Insufficiency. See ampicillin.

Pharmacology

	Dosage mg	Serum Concentration (mcg/ml)	Urinary Concentration (mcg/ml)	V_D L/kg	Normal t½ (hr)	Anuria t½ (hr)	Protein Bound (%)	Excreted Unchanged (%)
Adult	500	7–8	500–2500	0.4	1	16	Low	40–70

CSF penetration: concentrations of 5 to 10% of serum levels in the presence of inflamed meninges.

Adverse Reactions

Hypersensitivity Reactions. As with all penicillins, rash, urticaria, anaphylaxis, and serum sickness are possible, but are uncommon.

Gastrointestinal Disturbance. In children, amoxicillin may produce less diarrhea than ampicillin when given in oral suspensions.

Drug Interactions. See penicillin G.

Further Reading

Neu, H.C.: Amoxicillin. Ann. Intern. Med., *90*:356, 1979.

AMPHOTERICIN B (AmB)

This drug is available in vials containing 50 mg for reconstitution for intravenous use or irrigations and in lotion, cream, and ointment, in 3% concentration. (Fungizone)

Clinical Use. The topical formulations of amphotericin B are useful for the treatment of cutaneous or mucocutaneous candidiasis. The parenteral product is useful in the treatment of cryptococcosis, North American blastomycosis, disseminated candidiasis, coccidioidomycosis, histoplasmosis, mucormycosis, sporotrichosis, and aspergillosis. The drug is generally fungistatic, but may be fungicidal. It binds to sterols in the fungal cell wall and produces leakage of cellular contents. Irrigations of the urinary bladder may be performed in the treatment of candidal cystitis. Peritoneal lavage and intra-articular irrigation with amphotericin B may be useful in peritonitis and in septic arthritis.

Administration and Dosage. There is no universal agreement on the method of adminstration, the rate of infusion, or the daily or total dose of AmB. Further, the effect of the foregoing on systemic toxicity and nephrotoxicity has not been studied and is controversial. We recommend the following procedure:

Critically Ill Patients		Alternate Procedure	
Test Dose (1 mg)	Day 1	Test Dose (1 mg)	Day 1
0.25 mg/kg	Day 1	5 mg	Day 1
0.5 mg/kg	Day 2	10 mg	Day 2
0.75 mg/kg	Day 3	15 mg	Day 3
Increase dose or maintain, as tolerated by patient		20 mg	Day 4
		25 mg	Day 5
		30 mg	Day 6
		Increase dose by 5-mg increments or maintain, as tolerated by patient	

If Cr_S reaches 2.5 to 3.0 mg/dL, one should discontinue AmB for 24 to 48 hours, then reinstitute it at half the previous dose, and increase the daily dose by 5-mg increments to a tolerable level. The desired dose should be diluted in 250 to 500 ml of 5% dextrose in water and administered over 4 to 6 hours. Solutions do *not* need protection from light. Intrathecal administration is important in the treatment of coccidioidal meningitis and occasionally may be necessary in cryptococcal meningitis. Intrathecal injection: administration of AmB in 10% glucose solution, via the lumbar route, with immediate lowering of the patient into Trendelenburg's position, favors migration of drug to the occipital region. This procedure obviates the need for repeated cisternal punctures or for prolonged ventricular reservoir placement. This method appears to be efficacious, since the most severe coccidioidal lesions are at the base of the brain.

One should add 0.25 to 0.5 mg of AmB to 5 ml of 10% dextrose with 25 mg hydrocortisone, inject hydrocortisone 25 mg into LP site, and then inject hyperbaric AmB solution. The patient should be lowered immediately into Trendelenburg's position for 45 minutes.

For bladder irrigation, 25 to 50 mg of the drug should be added to 500 to 1000 ml of sterile water. One should *never add amphotericin B to saline-containing solutions.*

Dosage in Renal Insufficiency. Serum levels are not altered by impaired renal function. If the renal failure is felt to be due to the drug, then the following is recommended: When serum creatinine reaches 2.5 to 3.0 mg/dL, one should discontinue the drug for 24 to 48 hours, as the patient's condition allows, and reinstitute therapy at approximately half the previous dosage. Then daily dosage should be increased by 5-mg increments until the desired level is reached. This approach may ameliorate further decline in renal function. Alternatively, although this is unproven, administering the drug every other day, as soon as possible, may help to prevent nephrotoxicity.

Hemo- and peritoneal dialysis do not affect the clearance of AmB.