Practical Guide To ANTIMICROBIAL AGENTS

Michael Ginsberg, M.D., F.R.C.P.(C.)
Ira Tager, M.D., M.P.H.

Practical Guide To ANTIMICROBIAL AGENTS

Michael Ginsberg, M.D., F.R.C.P.(C)

Instructor in Medicine, Brown University
Clinical Instructor in Medicine, Harvard Medical School
Consultant in Infectious Disease, Roger Williams
General Hospital, Womens and Infants Hospital, and Veterans Administration Hospital
Providence, Rhode Island

Ira Tager, M.D., M.P.H.

Assistant Professor of Medicine
Harvard Medical School
Peter Bent Brigham Division of the Affiliated Hospitals, Inc.
Boston, Massachusetts

WILLIAMS & WILKINS
Baltimore/London

Made in the United States of America

Library of Congress Cataloging in Publication Data

Ginsberg, Michael.
Practical guide to antimicrobial agents.

Includes index.
1. Anti-infective agents. 2. Antibiotics. I. Tager, Ira, joint author. II. Title. [DNLM: 1. Antibiotics. 2. Anti-infective agents. QV350.3 G493p]
RM262.G56 615'.329 79-17016
ISBN 0-683-03529-0

Composed and printed at the
Waverly Press, Inc.
Mt. Royal and Guilford Aves.
Baltimore, Md. 21202, U.S.A.

PREFACE

This book is designed to provide detailed, practical information on the use of antimicrobial agents in children (excluding neonates) and adults. It is not a reference textbook but uses an outline format to provide rapid answers to the many clinical questions which arise in the day-to-day selection and use of antimicrobials. Each outline presents information on the clinically important aspects of spectrum, pharmacology, route+dosage, drug-drug interactions, toxicity, and toxicity monitoring. Pharmacologic parameters such as drug half-life and volume of distribution which do not have direct clinical relevance, have been intentionally omitted. Annotated references are provided at the end of each chapter for those who wish to review primary sources of data in more detail.

A series of outlines for the diagnostic evaluation and treatment of selected infectious diseases is also provided. The diseases presented have been selected because they are either very common and/or, in the case of meningitis, often lead to questions concerning proper diagnostic evaluation and treatment. Antimicrobials recommended for a given disease are cross-referenced so that the reader can quickly locate needed drug information related to a clinical problem.

Appendix A provides an alphabetized list of antimicrobials by brand name, generic name, and the page on which each is found. Appendix B provides an alphabetized list of antimicrobials by generic name and the page on which each is found. With the use of one of the appendices, information for any antimicrobial can be quickly located.

Four tables are also provided. They summarize information on the dialysance of antimicrobials, the excretion of antimicrobials in breast milk, and the transplacental passage of these drugs. No tables on dosage modifications necessary in renal failure or hepatic failure are provided. Rather, this information is included in the "Modification" section of "Route and Dosage" for each individual drug.

It is hoped that the organization and content of the book will make it a useful guide in the day-to-day practice of medicine, the purpose for which it is primarily intended. However, it is also anticipated that sufficient detail has been provided so that the book can also be used as a primary reference source for medical students and physicians who wish to familiarize themselves with the use of particular antimicrobial agents.

MICHAEL GINSBERG
IRA TAGER

CONTENTS

PENICILLIN

When organisms are susceptible, penicillin is always the drug of choice because of its potency, narrow spectrum and remarkably few adverse effects.

SPECTRUM

Prophylaxis

Rheumatic Fever—Benzathine penicillin 1,200,000 units i.m. monthly

***Streptococcus viridans* Endocarditis**—Na^+ or K^+ penicillin G 2,000,000 units i.m.
Procaine penicillin 600,000 units i.m.
Streptomycin 1 g i.m.
(or gentamicin 2 mg/kg i.m.)
All given 30 min before the procedure
OR
Penicillin V 3 g p.o. before dental work followed by 500 mg q6h × 2 days

Therapy

Gram-Positive Cocci—Sensitive

Streptococcus pneumoniae (pneumococcus)
All streptococcal species (use with an aminoglycoside for systemic infections with enterococci)
Staphylococcus aureus (non-penicillinase producing)

Gram-Negative Cocci—Sensitive

Neisseria gonorrheoae (gonococcus) (rarely resistant at present)
Neisseria meningitidis (meningococcus) (for treatment only—never for prophylaxis)

Aerobic Gram-Negative Bacilli—Sensitive **Resistant**

Streptobacillus moniliformis All others
Pasteurella multocida

Anaerobes—Most sensitive except *Bacteroides fragilis*: for practical purposes use for all anaerobic infections originating from mouth anaerobes ("above the diaphragm") e.g., lung abscess; *NOT* for those originating from large bowel anaerobes ("below the diaphragm"), e.g., intra-abdominal sepsis

Gram-Positive Bacilli—Sensitive	**Resistant**
Bacillus anthracis	Other *bacillus* sp.
Corynebacterium sp.	*Clostridium ramosum*
Listeria monocytogenes	
Erysipelothrix	
Clostridium sp. (except *ramosum*)	

Others—Sensitive	**Resistant**
All treponemes (syphilis, yaws, pinta, bejel)	*Nocardia*
Leptospira	*Mycobacterium*
Actinomyces sp.	*Mycoplasma*
	Chlamydia
	Rickettsia

PHARMACOLOGY

Absorption + Levels

	i.v.	i.m.	p.o.
Na^+ or K^+ penicillin G (benzyl penicillin G)	Peak depends on dose and rate of infusion; 4–6 hr: not detectable	Dose 1 million units Peak: 30 min: 12 μg/ml 4–6 hr: not detectable	Irregular absorption; destroyed by gastric acid
Procaine penicillin	Never	Dose: 300,000 units Peak: 2 hr: 1.6 μg/ml 12 hr: 0.2 μg/ml Duration: 12–24 hr	Never
Benzathine penicillin	Never	Dose: 2,400,000 units Day 14: 0.12 μg/ml Duration: 1–4 weeks	Never
Penicillin V* (phenoxymethyl)	Never	Never	Dose: 250 mg Peak: 30–60 min: 2–3 μg/ml Duration: 4–6 hr

* Other phenoxy penicillins include phenoxyethyl-, phenoxypropyl- and phenoxybenzyl-penicillin. These are generally less active than penicillin V.

Therapeutic Levels—Most organisms which are sensitive are killed by ≤1 μg/ml

Tissue Levels—*Adequate*: Urine, serum, synovial, pleural, pericardial and ascitic fluids

Borderline: Cerebrospinal fluid (usually adequate when meninges inflamed)

Inadequate: Obstructed biliary tract

Mechanism of Action—Bactericidal. Inhibits cell wall synthesis in multiplying bacteria

Metabolism—Up to 30% inactivated by the liver

Excretion—*Renal* ≥70% as active drug plus metabolites by glomerular filtration and tubular secretion

ROUTE AND DOSAGE

Adults: **i.v.:** Na^+ or K^+ penicillin G 250,000–2,000,000 units or more q4–6h (more frequent injections, e.g., q2h in meningitis)

i.m.: Na^+ or K^+ penicillin G; Painful

Procaine penicillin:	Pneumococcal pneumonia	300,000–600,000 units q12–24h
	Uncomplicated gonorrhea	4,800,000 units once with probenecid 1 g
Benzathine penicillin:	Strep throat	1,200,000 units once
	Rheumatic fever prophylaxis	1,200,000 units monthly
	Incubating, primary and secondary syphilis	2,400,000 units once
	Latent, tertiary, and unknown duration syphilis (except neurosyphilis)	2,400,000 units q week × 3

p.o.: Na^+ or K^+ penicillin G 250,000–500,000 units q6h (hydrolyzed by stomach acid; should not be used)

Penicillin V 250–500 mg q6h

Children: **i.v.:** Na^+ or K^+ penicillin G 25,000–400,000 units/kg/day divided into 4 or 6 equal doses

i.m.: Procaine penicillin 25,000–50,000 units/kg/day in a single dose or divided into 2 doses

Benzathine penicillin G 300,000–1,200,000 units total dose

p.o.: Penicillin G 25,000–50,000 units/kg/day divided into 4 equal doses (hydrolyzed by stomach acid; should not be used)

Penicillin V 15–30 mg/kg/day divided into 4 equal doses

Modifications: (1) *Probenecid*—Excretion blocked by probenecid, so serum levels will be doubled and duration prolonged

(2) *Impaired Renal Function*—No modification for mild or moderate renal failure; in severe renal failure ($C_{Cr} \leq 10$ ml/min), halve the dose and extend interval to q8–12h

(3) *Cardiac Failure, Renal Failure, and Fluid and Electrolyte Disorders*—
Na^+ penicillin G: Na^+ content: 1.7 mEq Na^+/1,000,000 units
K^+ penicillin G: K^+ content: 1.5 mEq K^+/1,000,000 units

(4) *Impaired Liver Function*— No modification necessary

DRUG-DRUG INTERACTIONS

None, except probenecid (see above)

TOXICITY

Hypersensitivity—Immediate: anaphylaxis, urticaria, bronchospasm
Later: laryngeal edema, serum sickness, erythema nodosum, erythema multiforme, Stevens-Johnson syndrome, exfoliative dermatitis, maculopapular rash

Massive Doses of Penicillin G (10 or 20 million units/day or more)

Central Nervous System—Convulsions, coma

Renal—Interstitial nephritis (hematuria, ↑Cr, ↑BUN, fever, eosinophilia, *eosinophiluria*)

Hematologic—Hemolytic anemia

Procaine Penicillin G—Procaine moiety may cause anxiety reaction, feeling of impending death lasting 15–30 min

Penicillin V—Nausea, diarrhea, oral thrush

TOXICITY MONITORING

History—Baseline: penicillin allergy

Physical Examination—Each visit: rash

Laboratory Tests—None

REFERENCES

1 **Sabath LD:** Phenoxymethyl penicillin and phenethecin. *Med Clin North Am* 54: 1101–1111, 1970 (Concise comparison of penicillin V with benzyl penicillin G including comparative sensitivities and pharmacokinetics; extensive bibliography)

2 **Adkinson NF, et al:** Routine use of penicillin skin testing on an inpatient service. *N Engl J Med* 285: 22–24, 1971 (Demonstrates unreliability of history of penicillin allergy for predicting anaphylactic and accelerated reactions; illustrates potential usefulness of skin testing for penicillin allergy)

3 **Green RL, et al:** Elevated plasma procaine concentrations after administration of procaine penicillin G. *N Engl J Med* 291:223–226, 1974 (Documents an uncommon but important complication of procaine penicillin—procaine toxicity)

4 **Bryan CS, et al:** "Comparably massive" penicillin G therapy in renal failure. *Ann Intern Med* 82: 189–195, 1975 (A formula and schedule for high level penicillin G therapy in renal failure)

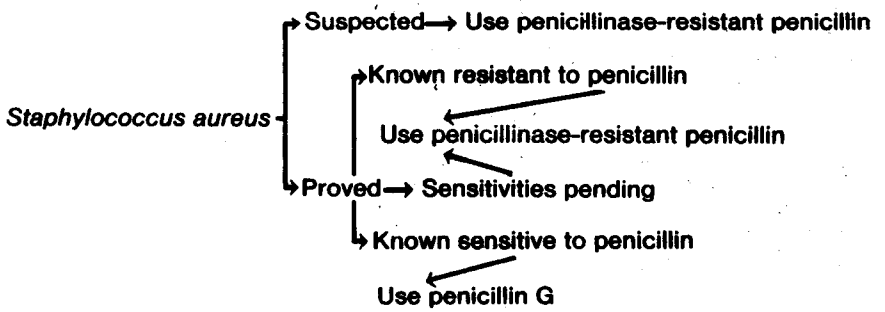
5 **Fossieck B, et al:** Neurotoxicity during intravenous penicillin. A review. *J Clin Pharmacol* 14:504–512, 1974 (Comprehensive review of neurotoxicity including clinical literature review)

6 **Idsoe O, et al:** Nature and extent of penicillin side-reactions, with particular reference to fatalities from anaphylactic shock. *Bull WHO* 38:159–188, 1968 (Extensive review of allergic reactions to penicillin including details of patients with anaphylaxis)

7 **Galpin JE, et al:** Acute interstitial nephritis due to methicillin. *Am J Med* 65: 756–765, 1978 (Suggests value of Wright's stain of urine for eosinophiluria in diagnosis of this disease entity)

PENICILLINASE-RESISTANT PENICILLINS

The *only* indication for penicillinase-resistant penicillins is the treatment and, in certain situations, prophylaxis of *staphylococcal infections.*



SPECTRUM

Generally Sensitive	Variably Resistant	Generally Resistant
Staphylococcus aureus	Enterococci	*Escherichia coli*
Staphylococcus epidermidis	*Neisseria gonorrhoeae* (gonococcus)**	*Klebsiella* sp.
Streptococcus pyogenes (Group A, β hemolytic streptococci)*	*Neisseria meningitidis* (meningococcus)**	*Enterobacter* sp.
*Streptococcus viridans**	*Bacteroides melaninogenicus***	*Proteus* sp.
Streptococcus pneumoniae (pneumococcus)*	*Fusobacterium* sp.**	*Pseudomonas* sp.
	Peptococcus sp.**	*Bacteroides fragilis*
	Peptostreptococcus sp.**	*Veillonella* sp.

* Penicillin is the therapy of choice for these organisms. However, when a penicillinase-resistant penicillin is used presumptively because of the possible presence of *S. aureus*, even *moderate doses* can be expected to successfully treat these organisms.

** Penicillin (or ampicillin) is the therapy of choice for these organisms. However, when a penicillinase-resistant penicillin *in high doses* is used presumptively because of the possible presence of *S. aureus*, infections caused by these organisms should also be effectively eliminated. For example, high dose oxacillin or nafcillin therapy should provide adequate therapeutic levels for the anaerobes involved in aspiration pneumonia.

** A penicillinase-resistant penicillin is *not* adequate therapy for penicillinase-producing *N. gonorrhoeae* (gonococcus).

PENICILLINASE-RESISTANT PENICILLINS