Infectious Diseases in Obstetrics and Gynecology

Gilles R. G. Monif, M. D.

INFECTIOUS DISEASES IN OBSTETRICS AND GYNECOLOGY

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PREFACE

There has long been a need for a single source of information dealing with infectious diseases as they affect the pelvis, the pregnant woman, and her conceptus.

The limited involvement of various disciplines with the pelvis has been a significant barrier to effective dialogue in this area. Most texts on infectious disease emphasize the major aspects of infection which often do not involve the female genital tract. Too often the discussion of possible genital involvement has been presented in a markedly condensed form. The purpose of this book is to evoke effective dialogue for the obstetrician–gynecologist, particularly in those areas where the natural history of infection differs from that observed in nonobstetrical patients or where infectious diseases are intimately involved with the practice of the discipline.

On organization, despite the extensive list of selected references immediately following the discussion of each infection or organism, for lucidity, the text has abandoned the standard format of carefully documented rhetoric of pros and cons. The mass of data emanating from immunology, internal medicine, microbiology, and pediatrics has been researched and digested by the authors and rendered into a pragmatic quantum for the reader.

The text is viewed as a specific adjunct, *not* as an alternative to existing books on infectious disease. It is hoped that information presented will lend cohesiveness to advances which have occurred in areas other than in obstetrics and gynecology and that the resulting augmented understanding of the process through which infectious diseases function will be translated into the everyday practice of obstetrics and gynecology.

G.R.G.M.

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CONTENTS

SECTION I

General Considerations

CHAPTER 1

Therapeutic Applications of Antimicrobial Agents

W. Eugene Sanders, Jr.

Infectious diseases have classically been conceptualized as a war between pathogenic microorganisms (the aggressors) and the host's resistance factors (the proud defenders of the homeland). Increasing morbidity was a reflection of an intensification of the conflict. Death or recovery marked the end of the battle. The analogy was extended and perpetuated by the hyperbolic designation of early antimicrobial agents, e.g., "magic bullets." This oversimplification was highly useful for teaching, but it mesmerized the public and even segments of the medical profession into acceptance of subsequent "wonder drugs"—penicillin, streptomycin, and tetracycline—as symbols of the ultimate victory of man over microorganism. The epithet "Infectious diseases are dead!" was widely sounded. Indications of the error of this assumption appeared almost immediately.

Three factors that account for the continuing, if not increasing, problems in recognition and management of infectious diseases are (1) perpetuation of a population of highly susceptible individuals; (2) a changing profile of microorganisms responsible for severe infections; and (3) increasing numbers and complexity in choices of antimicrobial agents. These events have proved conclusively that there are no true "magic bullets." It is doubtful that an agent will ever be discovered that is uniformly safe and effective against even a single genus of microorganisms. An infection in each patient must therefore be considered as a unique event. Variations in microorganism, host, activity of therapeutic agents, and their possible interactions must be weighed carefully in planning management of even the mildest infections.

This chapter is organized so as to be consistent with the classic analogy between infection and warfare. This is done not, as

in the past, to simplify but to emphasize the necessity for strict attention to detail and careful planning in ensuring an optimum chance for success.

The Enemy: Bacteria

Bacteria are complex creatures with both striking similarities to and profound differences from mammalian cells. Areas of unique structure, e.g., cell wall, or function, e.g., biosynthesis of folic acid, in bacteria have proved to be especially vulnerable to chemotherapeutic attack. However, all agents that affect these unique sites are not uniformly devoid of toxicity for mammalian tissues, despite apparent differences. On the other hand, a few agents that affect sites in bacteria common to host cells are relatively free of serious toxicity in man in the absence of excessive accumulation of drug in serum.

In general, bacteria are remarkably adaptable. Short generation times, high mutation rates, and occasional intergeneric transfer of genetic material have facilitated the emergence of drug resistance. Widespread use of antimicrobial agents has provided a selective advantage for these resistant strains in patients and in their environment. Advances in surgical procedures and therapeutic modalities have increased survival of patients suffering from diseases that predispose to bacterial invasion. Many therapeutic agents and devices themselves have been shown to *diminish* resistance to infection. Corticosteroids, immunosuppressive agents, antimetabolites, radiation therapy, and implanted prostheses are examples. Patients who are especially vulnerable have often succumbed to infection by normally nonpathogenic microorganisms residing in their indigenous microflora. Many of these microorganisms have been naturally resistant or have rapidly acquired resistance to antimicrobial agents. Each of these factors accounts in part for the expanding spectrum of microorganisms responsible for disease.

The Weapons: Antimicrobial Agents

The analogy between antimicrobial agents and weapons of defense is striking. Just as development of new destructive weapons is met with a frenzied search for defensive devices in a continuing upward spiral of risks and expense, so the expanding spectrum of drug-resistant microorganisms is countered with a proliferation of increasingly potent and expensive and potentially toxic antimicrobial agents. Effective utilization of this welter of new drugs becomes an increasingly difficult task for most practicing physicians. The problem is compounded by the marketing of an array of similar antimicrobial agents with minor pharmacological or biological differences, each promoted as "a unique advance in the chemotherapy of infection."

The physician's task in drug selection and administration may be simplified by demanding answers to a limited number of incisive questions posed to professional representatives or sought in promotional and scientific literature. The nature of these questions is the basis for the discussions of antimicrobial mechanisms, selection, administration, toxicity, and elimination that follow in this and subsequent sections.

Perhaps the most important and certainly the most frequently overlooked or unanswered question is "What is the mechanism of action of a given drug?" In the past, precise definition of the mechanism of action of many antimicrobial agents has followed their marketing and wide clinical use. Occasionally this may have been necessary because of the urgent clinical need for a specific drug. However, in many instances withholding distribution

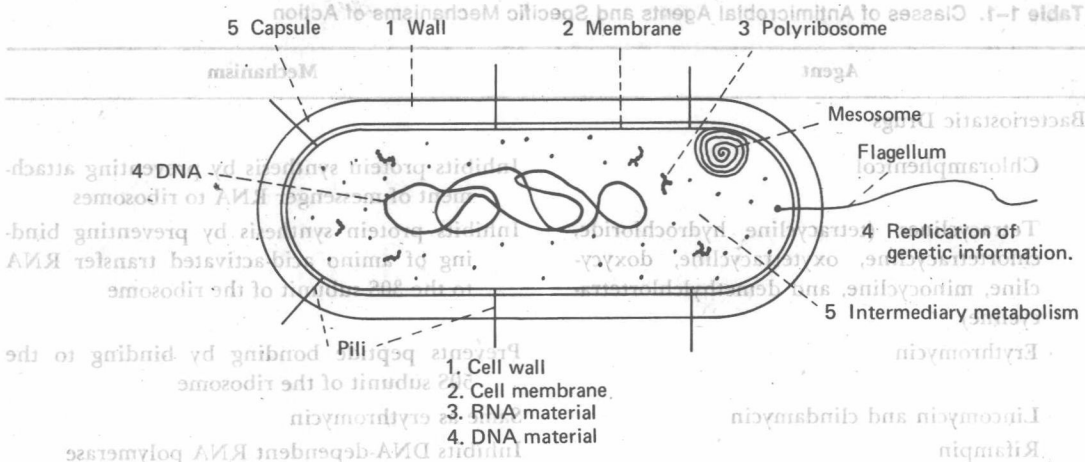

Figure 1–1. Morphologic sites of action of antimicrobial drugs. Antimicrobial agents that act at the sites enumerated in the figure are *1.* Agents that alter structure and function of the bacterial cell wall (the penicillins, the cephalosporins, vancomycin, bacitracin, ristocetin, and cycloserine). *2.* Agents that alter structure and function of the bacterial cell membrane (gramicidin, tyrocidin, the polymyxins, and colistin). *3.* Agents that act at the polyribosome or otherwise inhibit protein synthesis (chloramphenicol, the tetracylines, erythromycin, lincomycin, clindamycin, streptomycin, kanamycin, neomycin, gentamicin, and rifampin). *4.* Agents that impede replication of DNA (nalidixic acid and [in fungi] griseofulvin). *5.* Agents that impair intermediary metabolism (sulfonamides).

may have been both judicious and practical. Prior knowledge of mechanism of action permits prediction or anticipation of many characteristics of the drug that may not have been apparent in preclinical trials or promulgated in early promotional or scientific literature. Qualitatively similar toxic reactions and instances of cross resistance may be anticipated with drugs that act similarly. For example, had the mechanism of action of lincomycin been more widely known before its distribution, its remarkable similarity to erythromycin would have been more readily apparent and the subsequent instances of cross resistance and mutual antagonism would more likely have been predicted. The specific action of each new agent must therefore be compared with those of known antimicrobials before claims of uniqueness or potential usefulness can be judged with validity.

The sites of action of currently available antimicrobial agents are given in the legend of Figure 1–1, and specific mechanisms are listed in Table 1–1.

The Battle Plan: The Choice and Administration of Antimicrobial Therapy

Because of the great number and complexity of possible interactions between host, microorganism, and antimicrobial agents, the chosen therapeutic plan of attack should be devised as carefully and objectively as possible. Before embarking on a course of action, the physician should systematically seek answers to questions such as those posed in the following checklist.

Selection and Administration of an Antimicrobial Agent for Serious Bacterial Infections

1. Have all possible steps been taken to reach either a specific etiological diagnosis, or as limited a list of diagnoses to be differentiated as possible?
   a. Is the history and physical comprehensive and without omissions?

Table 1–1. Classes of Antimicrobial Agents and Specific Mechanisms of Action

Agent	Mechanism
Bacteriostatic Drugs	
Chloramphenicol	Inhibits protein synthesis by preventing attachment of messenger RNA to ribosomes
Tetracyclines (tetracycline hydrochloride, chlortetracycline, oxytetracycline, doxycycline, minocycline, and demethylchlortetracycline)	Inhibits protein synthesis by preventing binding of amino acid-activated transfer RNA to the 30S subunit of the ribosome
Erythromycin	Prevents peptide bonding by binding to the 50S subunit of the ribosome
Lincomycin and clindamycin	Same as erythromycin
Rifampin	Inhibits DNA-dependent RNA polymerase
Sulfonamides	Impairs folic acid synthesis by competing with paraaminobenzoic acid (sulfanilamide only inhibits carbonic anhydrase in *Neisseria*)
Bactericidal Drugs	
Penicillins (penicillins G and V, ampicillin, carbenicillin, methicillin, oxacillin, cloxacillin, dicloxacillin, and nafcillin)	Prevents cross-linking of the glycopeptide "backbone" of the cell wall, defects thus created expose the bacterial cell to osmotic lysis
Cephalosporins (cephalothin, cephaloridine, cephaloglycin, cephalexin, cephapirin, cefazolin, cephanone, and cephacetrile)	Same as penicillin
Aminoglycosides (streptomycin, kanamycin, neomycin, gentamicin, tobramycin, and sisomicin)	All induce misreading of the genetic code at the ribosomal level which results in incorporation of incorrect aminoacids into the growing peptide chain; this process or the defective proteins may be lethal to the cell; streptomycin may inhibit polymerization of aminoacids as well
Polymyxins (polymyxin B, colistin)	Cationic detergents with affinity for phosphate radicals which alter the osmotic barrier function of the cell membrane
Vancomycin, ristocetin, bacitracin	Inhibit glycopeptide synthetase which is responsible for condensation of glycopeptide component of cell wall
Cycloserine	A structural analogue of D-alanine which competes for sites on pentapeptide linkage of bacterial cell wall
Urinary Antiseptics (primarily bacteriostatic)	
Mandelamine (methenamine mandelate)	Liberates formaldehyde only in acid urine
Nalidixic acid	A structural analogue of purine nucleotides which impairs DNA synthesis
Nitrofurantoin	Uncertain

b. Has a Gram stain of infected material, free of normal flora, been made?
c. Have records been recently examined for results of cultures? They may be very useful in recurrent urinary tract infections.