Guidelines for the selection of antimicrobial therapy in pediatrics

An Essay submitted for partial fulfillment of master degree in pediatrics

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Abstract of essay

This study reviews the recent topic in selection of appropriate antibacterial therapy in Pediatrics and factors important in the selection of antimicrobial agents in infants and children. Recommendations for antibiotic therapy for a wide range of infections occurring in children are provided.

Keywords: Antimicrobial therapy / Selection of antibiotic in pediatrics / Pediatric infection

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CONTENTS

Abbreviations

AOM	Acute otitis media
AAP	American Academy of Pediatrics
AAFP	American Academy of Family Physicians
AHRQ	Agency for Healthcare Research and Quality
ARI	Acute respiratory infections
AWD	Acute watery diarrhea
β-lactamase	Beta Lactamase Acute watery diarrhea
CA-MRSA	Community acquired methicillin resistant S-aureus
CSF	Cerebrospinal fluid
CNS	Central nervous system
CAM	Complementary and alternative medicine
CXR	Chest x-ray
DNA	Deoxy ribonucleic acid
E.coli	Escherichia coli
EPEC	Enteropathogenic E.coli
ETEC	Enterotoxigenic E.coli
G6PD	Glucose 6 phosphate dehydrogenase
GAS	Group A streptococci
GBS	Group B streptococci
HA-MRSA	Hospital acquired methicillin resistant S-Aureus
IM	Intra-muscular
LRTI	Lower respiratory tract infection
MIC	Minimum inhibitory concentration
MRSA	Methicillin resistant S aureus

MRSE	Methicillin resistant S epidermidis
MEE	Middle-ear effusion
m RNA	Messenger ribo-nucleic acid
NA	Non specific action
nm	Nano-meter
OME	Otitis media with effusion
PBPs	Penicillin binding proteins
SI	Surgical infection
SSI	Surgical site infection
TMP-SMZ	Trimethoprim-Sulphamethoxazole
t RNA	Transfer ribo-nucleic acid
U.S.	United States
UTI	Urinary tract infection
URTI	Upper respiratory tract infection
WHO	World health organization

LIST OF TABLES

LIST OF FIGURES

Introduction

Selection of appropriate anti-infective therapy can be challenging to the pediatrician. It is not sufficient to know the likely pathogens causing the infection and which antibiotics have been successful in the past (Long and Dowell,2003).

It is also necessary to know prevalent antibiotic resistance patterns and the effect that treatment might have on promoting the development of resistance in the specific patient being treated and in the general population (Whitney et al.2000).

Determining the appropriate dose of antibiotics for children also can be difficult. Clinical studies evaluating antimicrobial pharmacokinetics in neonates (from extremely low birth weight to full term), infant, and children are few in number compared with studies performed in adults. Doses often are extrapolated from data derived from adult. Adverse event profiles also are based in large part on studies performed in preclinical animal toxicology models or in clinical trials conducted in older subjects (Craig, 1998).

The clinical relevance of understanding how antibiotics inhibit or kill pathogens at the site of infection, termed pharmacodynamic, has been integrated only recently into clinical investigations conducted in adults, similar studies in children to validate these concepts do not exist (Drusano, 2004).

This article reviews factors important in the selection of antimicrobial agents in infants and children. Recommendations for antibiotic therapy for a wide range of infections occurring in children are provided.

CHAPTER 1

Groups of antibiotics

Unlike physicians practicing in the 1940s, who had only sulfonamides and penicillin to treat infections, practitioners now choose from a broad (and sometimes overwhelming) number of antibiotics. However, trends in emerging antimicrobial resistance may force us to take a giant step backward to that frightening situation of the past of having bacteria that are essentially "untreatable" by any of our available antibiotics.

This article is an overview of some of the microbiology, pharmacology, and physiology critical to the rational use of antibiotics in today's practice. It summarizes the basic mechanisms of action of some commonly used antibiotics and briefly discusses the emergence of resistance to several common pathogens.

Structures of Bacteria Important to Antibiotic Action

The outermost component of most bacteria is the cell wall, a multilayered structure located external to the cytoplasmic membrane. The cell wall is composed of an inner layer of Peptidoglycan, a complex interwoven lattice of linear sugar (glycan) that are cross-linked by peptide chains. Peptidoglycan provides the rigid support by which the cell maintains its characteristic shape (Figure 1) (Ghuysen and Hakenbeck, 1994).

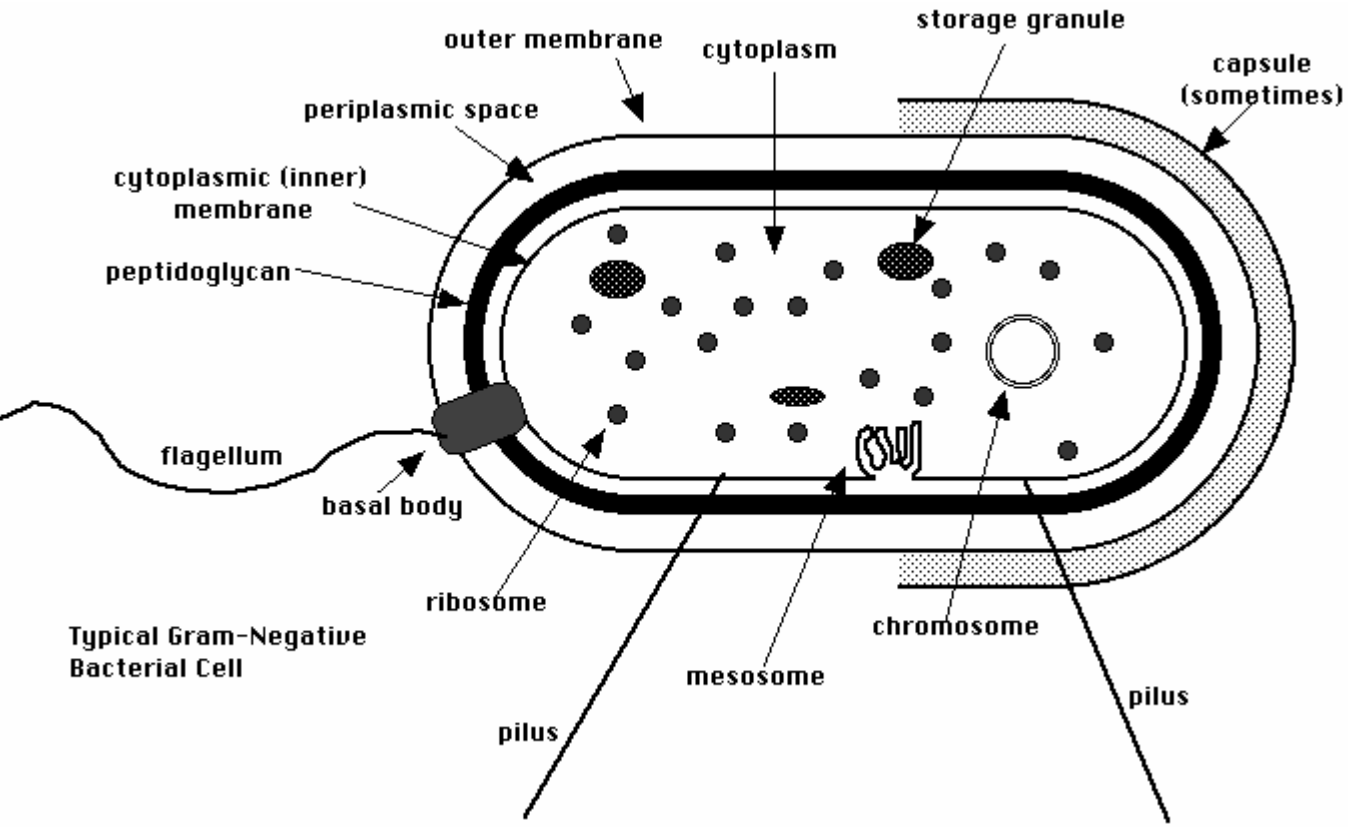

Figure1. Basic structure of the bacterial cell
(Ghuysen and Hakenbeck, 1994).

Gram-positive and Gram-negative bacteria differ in their cell wall structures. In Gram-positive organisms, the peptidoglycan layer is a thick (15 to 80 nm) multilayer and may have a thin layer of teichoic acid outside the peptidoglycan. In contrast, Gram-negative organisms have a thin (2 nm) single layer of peptidoglycan covered by a complex outer membrane layer composed of lipopolysaccharides, lipoproteins, and phospholipids. The outer membrane of Gram-negative bacteria contains porin proteins that act as channels to transport small molecules such as sugars, metals, vitamins, and antibiotics into the bacterial cell (Jawetz et al. 1989) (Rogers, 1983).

The cytoplasm of bacteria contains an inner nucleoid region composed of single-stranded circular DNA and matrix that contains ribosomes, nutrient granules, metabolites, and plasmids. Plasmids are double-stranded circular DNA molecules that can replicate independently of the bacterial chromosomes.

Most plasmids are extra chromosomal, but some are integrated into the bacterial chromosome. Plasmids occur in both Gram-negative and Gram-positive organisms and are an important source of genetic information that can convey resistance to various antibiotics (Figure 2) (Brooks, et al. 1991).

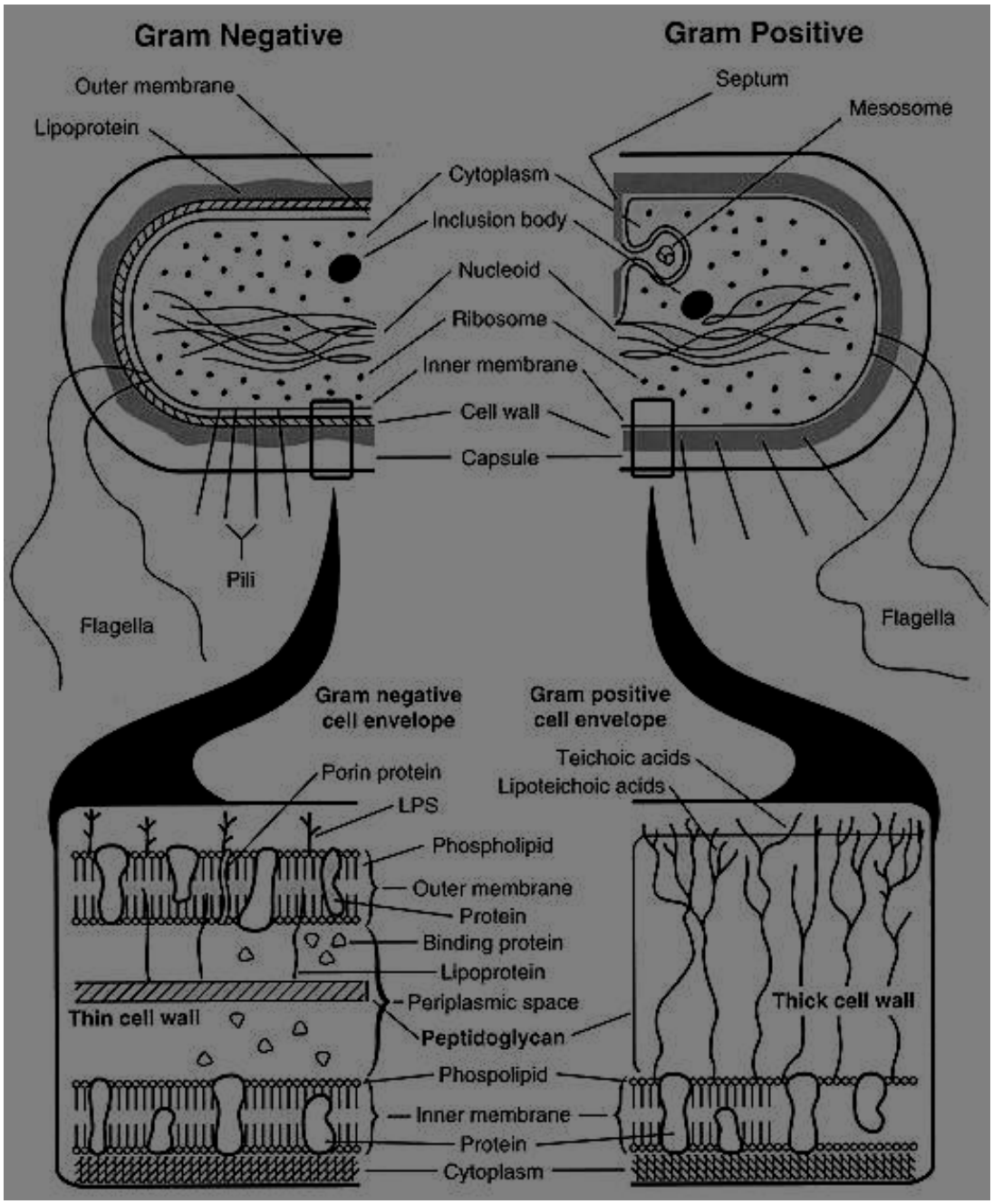

FIGURE2. Comparison of the thick cell wall of Gram-positive bacteria with the comparatively thin cell wall of Gram-negative bacteria. (Brooks, et al. 1991).

Selective Toxicity

An ideal antimicrobial agent would exhibit selective toxicity; that is, the drug would be harmful to the infecting microorganism without harming the host. Because peptidoglycan is present in bacteria but not in human cells, it is an excellent target for antibiotics. Similarly, antibiotics that affect protein synthesis take advantage of the differences in size and chemical composition of ribosomes from bacteria and eukaryotic organisms (i.e., those having a true nucleus surrounded by a nuclear membrane and multiple chromosomes, as in human cells). Other metabolic steps that occur in bacteria but not humans (e.g., synthesis of folic acid for nucleotides) also can be inhibited selectively by antibiotics (Gilman, et al. 1990) (Kucers and Bennett, 1987).

Bactericidal Versus Bacteriostatic Properties of Antibiotics

A favorable therapeutic outcome following the administration of a specific antibiotic depends on multiple factors, including those related to the bacteria (e.g., resistance mechanisms), the antibiotic (e.g., mechanism of action, ability to penetrate to the infected site, and spectrum of activity), and the host defenses (e.g., phagocytosis, opsonization, complement production) (Drusano, 2004).

When host defenses are maximally effective, the contribution of the antibiotic may be less important. For example, a bacteriostatic agent (e.g., chloramphenicol, erythromycin, clindamycin, and tetracycline) that slows or inhibits protein synthesis may be adequate when combined with the host's ability to opsonize and phagocytes bacteria. In contrast, a patient whose host defenses are impaired may require a bactericidal agent (e.g., penicillin, cephalosporin, aminoglycoside) that actually will kill or lyse the bacteria. Bactericidal agents (Table 1) generally are used to treat bacterial endocarditis, meningitis, and osteomyelitis as well as any

bacterial infections in neutropenia patients (Mulligan and Cobbs, 1989).

Table1. Classification of Antibiotics By Mechanism of Action

MECHANISM	DRUGS	ACTION*
Weaken bacterial cell wall and cause cell death		
Inhibit cross-linking of peptidoglycan	Penicillins, cephalosporins	Bactericidal
Activate autolytic enzymes (ie, autolysins)		
Inhibit other steps in peptidoglycan synthesis	Vancomycin	Bactericidal
Increase cell membrane permeability		
Cause leakage of cell contents	Polymyxin	NA
Inhibit protein synthesis		
Bind to 50S ribosome subunit	Chloramphenicol	Bacteriostatic
	Erythromycin	Bacteriostatic
	Clarithromycin	Bacteriostatic
	Clindamycin	Bacteriostatic
Bind to 30S ribosome subunit	Aminoglycosides	Bacteriocidal
	Tetracyclines	Bacteriostatic
Inhibit nucleic acid synthesis		
Inhibit nucleotide synthesis	Sulphonamides, Trimethoprim	Bacteriostatic
Inhibit DNA-dependent RNA Polymerase	Rifampicin	Bacteriocidal
Inhibit DNA super coiling and DNA synthesis	Quinolones	Bacteriocidal

*Note: Bacteriostatic agents may be bactericidal against some organisms at high concentrations.

(Mulligan and Cobbs, 1989).

Antibiotic Susceptibility

If the concentration of an antibiotic required to inhibit or kill the organism can be achieved safely in the affected tissue or fluid, a microorganism is considered sensitive to a particular antibiotic. However, if the concentration required is greater than what can be achieved safely, the microorganism is considered to be resistant to that antibiotic. Most in vitro sensitivity tests are standardized on the basis of drug concentrations that can be achieved safely in plasma and may not take into account increased drug concentrations that may occur at specific sites (e.g., bladder) or any local conditions that may affect the activity of the antimicrobial agent (Kucers and Bennett, 1987).

Mechanisms of Action of Antibiotics

For many antibiotics, the mechanism of action is not understood fully. However, it is known that antibiotics can act in the following ways: 1) Inhibit cell wall synthesis, 2) Alter the permeability of the cell membrane, 3) Inhibit protein synthesis, and 4) Inhibit nucleic acid synthesis (Gilman, et al.1990).

(I) a- WEAKEN CELL WALL BY INHIBITING CROSS-LINKING OF PEPTIDOGLYCAN

Penicillins and Cephalosporins

Penicillins and cephalosporins (beta-lactam antibiotics) are among the most widely prescribed antibiotics because of their safety profiles. The basic structure of penicillin consists of a five-member thiazolidine ring connected to a beta-lactam ring to which a side chain is attached. In contrast, the cephalosporins have a six-membered hydrothiazine ring connected to the beta-lactam ring. An intact beta-lactam ring structure is an essential requirement for the biologic and antibacterial activity of both penicillins and cephalosporins. New derivatives of the basic