Part One

INTRODUCTION

THE NATURE OF THE PRACTICE OF INFECTIOUS DISEASES

The practice of infectious diseases depends on the application of information, knowledge, skills, and judgment related to three areas, namely epidemiology, clinical medicine, and clinical microbiology. This book is intended to provide insights into infectious diseases in children, emphasizing the importance of these considerations.

The goal of clinical practice is to cure patients or, at least, to ameliorate their condition. The ultimate goal lies in a good or beneficial outcome, not only for the individual patient but also for the public. The outcome depends to a large extent on some kind of action being taken. For the individual this is usually therapeutic. For the public the action might entail tracing of exposed contacts, quarantining of exposed individuals, and providing vaccination or chemoprophylaxis. The action to be taken often, but not always, depends on an accurate diagnosis being made. It is important to remember that the ultimate goal does not lie in making an accurate diagnosis, nor in taking some action, but in obtaining a favorable outcome. There are circumstances in which the accurate diagnosis in an individual patient is not as important to that patient, for whom there may be no available therapy, as to the community.

COMPONENTS OF A DIAGNOSIS

Giving appropriate therapy often depends on making an accurate diagnosis. The diagnosis, like ancient Gaul, is divided into three parts (omnis diagnosis in tres partes divisa est):

1. Anatomic diagnosis, for example, the lung, the middle ear, the urinary tract.
2. Physiologic diagnosis. This describes functional disturbances, for example, respiratory failure, shock.

The physiologic diagnosis is important for determining what supportive care the patient requires. In patients with severe illness providing appropriate supportive care is more urgent than is providing antimicrobial therapy. For example, in a patient with septic shock, the most urgent matter is to restore adequate perfusion; in a patient with respiratory failure complicating pneumonia, the most urgent matter is to ensure adequate ventilation and oxygenation.

Making an anatomical and physiological diagnosis depends on the history, physical examination, and sometimes on laboratory and imaging tests.

3. Pathologic and/or etiologic diagnosis, for example, inflammation caused by *Streptococcus pneumoniae* or purpura fulminans caused by *Neisseria meningitidis*.

In the case of infectious diseases, the etiological diagnosis is represented by the microbiological diagnosis.

MICROBIOLOGICAL DIAGNOSIS

In infectious diseases making an etiologic or microbiological diagnosis is very important because specific therapy, where available, entails use of an antimicrobial agent.

The microbiological diagnosis can often be made based on the anatomic diagnosis. For example, if the diagnosis is otitis media, we can assume, based on previous studies of middle ear fluid of children with otitis media, that the likely causative organism is one of the following: *Streptococcus pneumoniae*, *Haemophilus influenzae*, or *Moraxella catarrhalis*. This principle can be applied to an infection at any anatomic site. An etiological diagnosis is usually difficult to make in the absence of an anatomic diagnosis.

RISK FACTORS FOR INFECTION

The microbiological diagnosis also depends on the **risk factors** that the patient has for acquiring a particular infection. Such risk factors can be considered in terms of (a) genetic factors, for example, sickle cell disease, and (b) environmental factors or the epidemiological circumstances in which the patient's infection was acquired. This constitutes the patient's **exposures**.

A list of possible exposures that should be inquired about is shown in Table 1. When obtaining a history about exposures, I have found it useful to explain to patients (or their parents) the purpose of the apparently bizarre questions that I intend to ask.

TAB. 1: Types of exposures to infectious agents.

Sick human beings	family, friends, day care, shelter for the homeless, immigrants, visitors from abroad, prison, military
Maternal infections	intrauterine (transplacental), intrapartum, postnatal
Animals	vertebrates – fish, amphibians, reptiles, birds, mammals arthropods – ticks, mosquitoes, fleas, lice, flies, mites
Travel	foreign or domestic; foreign-sounding names or accents should prompt enquiry about foreign travel
Occupation of patient or parents	
Recreational activities	sports, hobbies, sexual activity, drug abuse
Hospitalizations and visits to health care facilities	
Injections	legal and illicit, blood transfusions, vascular catheters
Surgery, foreign body insertions	
Immunizations	
Antimicrobial therapy	
Food and water sources	

There is an aphorism used in clinical medicine in the United States regarding the likelihood of a particular disease among a differential diagnosis: "when you hear hoofbeats, think of horses, not zebras." One of the messages of this book is:

"Think about zebras as well as horses, because whether horses or zebras are more likely depends on where you come from!" (Figure 1).

Furthermore, zebras are found in groups. Therefore, when individuals are exposed to exotic diseases, they may be exposed to more than one disease at the same time.

Patients with defects in their host defenses (genetic or acquired) are at risk for infections caused by certain microorganisms that are unlikely to infect normal hosts. Different host defense defects predispose to different kinds of infections. Table 2 lists some host defense defects and infections to which they predispose.

METHODS FOR MAKING A MICROBIOLOGICAL DIAGNOSIS

There are several different methods for confirming a microbiological diagnosis, which are summarized in Table 3. They can be divided into (a) direct methods, in which the organism is visualized, cultured, or a component of

FIG 1. Zebras.

the organism is detected, for example, antigen, DNA; and (b) indirect methods, which depend on the host's response to the infection (i.e. serological methods). The direct methods are undergoing significant changes due to the rapid advances being made in our ability to detect microbial nucleic acid.

In making a microbiological diagnosis, the optimal site for obtaining material for diagnosis is from the site of infection, when possible. Although this may seem intuitive, it is remarkable how frequently this principle is not followed. This principle is frequently referred to as "Sutton's Law," named for the bank robber, Willie Sutton, who, when asked why he robbed banks, replied, "Because that's where the money is."

In the diagnosis of infections, in general, the sicker the patient is, the less room there is for making an error in diagnosis, and consequently the more important it is to make a microbiological diagnosis. This may necessitate invasive procedures. For example a normal child with otitis media does not require a myringotomy to obtain middle ear fluid for culture. Most children with this condition recover with or without antimicrobial therapy. On the other hand, a child who has recently undergone bone marrow transplantation and has a rapidly progressive pneumonia might need to undergo an invasive procedure such as a bronchoalveolar lavage or a lung biopsy in order to determine the causative organism, considering the wide variety of possible pathogens and the toxicity of some of the therapeutic agents that might be indicated.

TAB. 2: Host defense defects and infections to which they predispose.

Defect	Infection/Organism
Skin	
Atopic dermatitis	*Staphylococcus aureus*, *Streptococcus pyogenes*
Burn	*Staph. aureus*, *Strep. pyogenes*, *Pseudomonas aeruginosa*
Varicella	*Strep. pyogenes*, *Staph. aureus*
Vascular catheter	staphylococci, *Candida* sp., enterococci, enteric bacilli
Endotracheal intubation	pharyngeal flora, Gram-negative bacilli
Urinary catheter	Gram-negative bacilli, enterococci, *Candida* spp.
Blood diseases	
Sickle cell disease	*Streptococcus pneumoniae* sepsis, salmonella osteomyelitis
Iron overload	enteric rod sepsis, especially *Yersinia enterocolitica*
Cancer chemotherapy with neutropenia	staphylococci, streptococci, Gram-negative rods, fungi
Transplant	herpes group viruses, adenovirus, many different bacteria, including mycobacteria and *Nocardia* spp., *Listeria monocytogenes*, fungi, *Pneumocystis jiroveci*, and *Toxoplasma gondii*
Congenital Immunodeficiencies	
Immunoglobulin deficiencies	pyogenic bacterial infections, pneumonia, sinusitis
Combined immunodeficiencies	bacterial infections, severe viral infections, *Pneumocystis jiroveci*
Chronic granulomatous disease	infections with staphylococci, Gram-negative bacilli, mycobacteria, fungi
HIV infection	*Pneumocystis jireveci*, mycobacteria, *Candida* spp., Cytomegalovirus, bacteremia

PRINCIPLES OF MANAGEMENT OF PATIENTS WITH INFECTIOUS DISEASES

The following five main principles should be considered in the management of patients with infections, not all of them necessarily applying to all cases:

Supportive care. This is the most important aspect to consider, and, in patients with life-threatening infections, it is the aspect that must be addressed immediately. For example, in a patient with shock due to severe bacterial infection, the most important first step in management is to ensure adequate tissue perfusion with intravenous fluid. In a patient with respiratory failure due to pneumonia, the most important first step in management is to ensure adequate oxygenation and ventilation.

TAB. 3: Methods for making a microbiological diagnosis.

A. Direct visualization of the organism	
Electron microscopy for viruses	seldom performed
Gram stain for bacteria	very useful; rapid, cheap, semi-quantitative
Wet preparations	bacteruria, *Trichomonas vaginalis*
unstained, mixed with saline	*Entamoeba histolytica*, ova, fungi
dark field	spirochetes
cleared with 10%KOH	fungi
Acid-Fast stain	Mycobacteria
Cytology	
Papanicolaou stain	viral inclusions, viral cytopathic effects
Silver stain	*Pneumocystis jiroveci*, fungi
Gram stain	bacteria
Immunostaining	viruses, bacteria, fungi, parasites
Blood smears (stained with a Romanowsky stain – Wright's, Leishman's, Giemsa)	*Plasmodium* spp., *Trypanosoma* spp., *Babesia* spp., relapsing fever *Borrelia* spp., morula of *Ehrlichia* spp., *Bartonella bacilliformis*, microfilaria
Histology – sections stained with hematoxylin and eosin and the above-mentioned stains	
B. Culture of the organism – this is the "gold" standard for detection of many organisms, especially bacteria and viruses	
Tissue culture	viruses, *Chlamydia* spp., *Rickettsia* spp.
Nutrient-containing agar and broths	bacteria, fungi
Living tissue e.g. eggs	viruses, *Rickettsia* spp.
Animal inoculation	this is very seldom performed
C. Detection of microbial antigens in body fluids and tissues	
D. Detection of nucleic acid in body fluids and tissues, by signal amplification, nucleic acid amplification (e.g. polymerase chain reaction), and several other methods	
E. Serology – this detects the host's response to the infection, that is the presence of antibodies. Although not the optimal way in which to diagnose an infection, in some infections it is the only way. There are many different methods for detecting antibody responses to infection. These include the following:	
Neutralization	
Complement fixation	
ELISA	
Immunofluorescence	
Hemagglutination	

READING: Winn WC Jr, Allen SD, Janda WM, Koneman EW, Procop GW, Schreckenberger PC, Woods GL: Molecular Microbiology. Chapter 4 in Koneman's Color Atlas and Textbook of Diagnostic Microbiology. 6th edition. Lippincott William and Wilkins, Philadelphia, 2006, pp. 132–165.

Antimicrobial therapy. This is specifically intended to kill or inhibit the growth of invading microorganisms. For many patients with infections, especially viral infections, there is currently no available antimicrobial therapy. The principles for choosing antimicrobial agents are discussed below.

Surgery. This may be necessary for therapy or for diagnostic purposes. It includes aspirating or biopsying infected lesions to obtain material for staining, culture, or histology, and draining of abscesses.

Addressing the interests of the community. The community may be the family, friends, school attendees, other patients in a hospital or clinic, or members of the broader community of the city, country, or world. For example, when a case of tuberculosis is diagnosed, the local health department should be informed so that contact tracing can be instituted. When a child with a contagious illness is admitted to hospital, specific isolation precautions should be instituted.

Prevention. For the most part this entails immunization. Although this will have failed if a patient is diagnosed with a preventable disease, making such a diagnosis should lead to an examination of the possible reasons why this failure occurred and how the problem can be rectified to prevent other patients acquiring the same illness.

The Gram Stain

Remember, Oh! The Gram stain test.
It's quick, it's cheap, it is the best!

Whenever you have secretions,
Exudates or draining lesions.
If its closed, suck some juice,
Then a diagnosis you'll deduce.

Make a smear (not too high),
On a slide, and let it dry.
After each step you must rinse,
Purple, brown – it's a cinch.
Clear (few secs), then safranin.
Wash and dry: now examine.
Optimize the light. For vision
Use the oil immersion.

Cells are red, and germs – all kind
Purple (pos), Pink (neg) – you will find.

Remember, Oh! To hold in awe
The verity of Sutton's Law,
Which from a robber may sound funny
In diagnostics:
GO FOR THE MONEY!

Don't throw pus, sputum, or pee down the drain
Until you have first done –
A GRAM STAIN
With some purple, then brown; then red after alcohol
You can Gram stain anything, ANYTHING,
ANYTHING AT ALL.

PRINCIPLES OF CHOOSING ANTIMICROBIAL THERAPY

Antimicrobial therapy is different from other forms of medical therapy in that its goal is to affect a biological process in an invading microorganism, thus inhibiting its growth or resulting in its death. The goals of other forms of medical therapy are directed at influencing a physiologic process in the patient. The use of antimicrobial agents can result in microorganisms developing resistance to such agents. Microorganisms in an individual patient can spread from that individual to colonize or infect another individual. Any antimicrobial resistance that has developed among microorganisms within this host will thus be carried to the new host. Thus antimicrobial resistance can be spread to other members of the community and, in fact, to other generations of hosts. Therefore prescribing antimicrobial agents carries with it an awesome responsibility and should be carried out judiciously.

Once it has been determined that the patient has or probably has an infection, AND that antimicrobial therapy is indicated, the main questions to be answered are

1. What is (are) the most likely causative organism(s)?
2. What are their most likely antimicrobial susceptibilities?

These are the most important questions to ask, and the most challenging to answer, particularly in situations in which a specific diagnosis has not been made (a frequent situation in pediatrics). The answer to question 1 lies in the diagnosis, discussed above. The answer to the question regarding antimicrobial susceptibilities is determined by local epidemiology and the patient's history of prior exposure to antimicrobial agents. The antimicrobial susceptibilities may vary from country-to-country, community-to-community, hospital-to-hospital, and ward-to-ward. For example ampicillin might be indicated for empiric treatment of a patient with an *E. coli* infection acquired in a community where the resistance rate of *E. coli* to ampicillin is 5%, whereas it would not be indicated for someone with the same infection acquired in a hospital ward where the resistant rate is 70%. Once a causative organism has been isolated and its antimicrobial susceptibilities are known, antimicrobial therapy usually becomes fairly simple.

The next question to be asked is:

3. What is the most appropriate agent to use?

In actually choosing a specific antimicrobial agent, several factors must be considered. The overriding principle in choosing therapy, however, is the following: USE AS NARROW A SPECTRUM AGENT AS POSSIBLE.

The other factors that should be taken into account are as follows:

1. *Spectrum of antimicrobial activity.* The drug must have the necessary spectrum as determined by questions 1 and 2 above.

2. *Severity of infection.* This determines the balance of risks between treatment and no treatment or between treatment with one drug and another, which is, in turn, determined by the adverse effect profile of the drugs. The severity of the infection also determines the speed with which an effect is necessary and, therefore, also influences the route of drug administration. For example, it would not be appropriate to use chloramphenicol, which has the rare side effect of causing aplastic anemia, to treat a patient with simple otitis media, but it might be appropriate to use it for treating a patient with a brain abscess. Similarly it would not be appropriate to use intravenous cefotaxime for treating a child with simple otitis media thought to be caused by *Streptococcus pneumoniae*, but it would be appropriate to use such therapy in a toxic-appearing patient with lobar pneumonia suspected to be caused by the same organism.

3. *The pharmacokinetics of the drug.*

   (a) *The distribution of the drug.* The drug must attain an adequate concentration at the site of infection to eliminate the infection. Because different drugs penetrate different tissues to different degrees, infections caused by the same organism but at different sites might necessitate the use of different drugs. For example, clindamycin would be suitable for treating a patient with a lung abscess but not for a patient with meningitis caused by the same organism because it does not enter the cerebrospinal fluid in a significant concentration.

   (b) *The elimination of the drug by metabolism or excretion.* Dysfunction of the liver or kidney might interfere with the elimination of certain drugs. In such cases the drug might accumulate to toxic concentrations. This might prevent the drug from being used safely.

4. *The route of administration.* This is usually determined by the severity of infection (see 2 above) and the possible routes for administration of the specific drug. Several drugs, especially those used for treating patients

with severe illness, can be given only intravenously, for example, vancomycin. This places a constraint on the use of this drug.

1. *Drug–drug interactions.* Many patients, especially those with underlying illnesses, receive multiple drugs. Several drugs, including "over-the-counter" preparations, interfere with the pharmacokinetics of other drugs, resulting in their blood levels being inadequate or excessive. The general mechanisms by which these interactions occur are as follows:

   (a) Interference with oral absorption, for example, antacids, such as aluminum hydroxide, interfere with the absorption of fluoroquinolones.
   (b) Interference with hepatic metabolism. This applies particularly to drugs that are metabolized by the cytochrome P450 enzyme systems. Drugs that induce hepatic enzymes, for example, rifamycins and anticonvulsants, speed up the metabolism of some other drugs, for example, corticosteroids and warfarin, resulting in reduced effects. Some drugs, for example, erythromycin, inhibit the metabolism of other drugs, for example, theophylline, resulting in them reaching toxic levels in the blood.

      Antimicrobial agents that are frequently associated with drug–drug interactions include the rifamycins, imidazole antifungal agents, macrolides, and antiretroviral protease inhibitors.
   (c) Additive injury to the kidney, resulting in decreased excretion of the drug, for example, a combination of an aminoglycoside and vancomycin.

2. *Cost*. When multiple drugs are equivalent in the above characteristics, the cheapest option should be used.

PRINCIPLES OF ADDRESSING PUBLIC HEALTH INTERESTS

Members of a community often have an interest in the diagnosis of an infection in an individual because they may be at risk for acquiring the same infection. There are several situations in which this may occur, but essentially there are two main reasons for community interest:

(a) the patient may be the index case of a broader outbreak or represent a sentinel case, indicating the local presence of the disease. For example, a child is generally the victim of tuberculosis spread from an adult. Therefore the diagnosis of tuberculosis in a child indicates the presence of an adult source who must be sought, so that he or she can be treated, so that spread to additional individuals is interrupted, and so that other individuals already infected can be identified and treated. The diagnosis