Essentials of Clinical Infectious Diseases
Second Edition

William F. Wright

New bonus chapter on COVID-19

Updated second edition of the concise but comprehensive handbook of clinical infectious disease for students, residents, primary care medical providers, nurses, and PAs. Written in outline format with short, focused chapters, the book presents a systematic method for understanding basic mechanisms, establishing a diagnosis, and implementing appropriate treatment for commonly encountered problems. Essentials of Clinical Infectious Diseases, Second Edition begins with a general framework covering clinical reasoning, antimicrobial agents and microbiology, and antimicrobial stewardship. Individual chapters devoted to the broad range of infectious diseases are organized by body system and feature targeted presentation of pathogenesis and risk factors, microbial causes, clinical manifestations, patient work-up, diagnostic criteria, and medical, antimicrobial, and surgical management. The book also addresses important related topics including fever and neutropenia, approach to evaluating ectoparasite-related infections, sepsis and travel medicine, infection control, and hospital epidemiology. Designed for busy practitioners at any level looking to sharpen the clinical problem-solving skills required to provide the highest quality care to patients with infectious diseases.

Key Features
- Includes a new bonus chapter that addresses severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), also known as coronavirus disease 2019 (COVID-19)
- Presents core clinical infectious disease topics in concise easy-to-read format
- Revised and updated to reflect recent developments in the field consistent with evidence-based literature and current clinical practice guidelines
- Six new chapters on Lyme disease, anorectal infections, travel medicine, dental infections, antimicrobial stewardship, and clinical reasoning and statistics
- Focus on the approach to evaluation and management of the patient
- Incorporates essential antimicrobial therapy information with adult, pediatric, and OB-GYN dosing considerations

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William F. Wright

An Imprint of Springer Publishing

New bonus chapter on COVID-19
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To Susan—my beautiful wife, best friend, and the wind beneath my wings. I am the luckiest man in the world to be married to a magnificent and brilliant woman like you. Sharing our life and love along this journey together is a blessing beyond words. I am grateful for your unwavering love, faith, and support. This book is affectionately dedicated to you, without whom this second edition would not have been completed.
CONTENTS

Contributors  xiii
Preface  xvii
Acknowledgments  xix

I. INTRODUCTION TO CLINICAL INFECTIOUS DISEASES

1. Introduction and Basics of Clinical Reasoning  1
William F. Wright

2. Introduction to Antimicrobial Stewardship  10
Susan L. DeBiase
William F. Wright

3. Introduction to Antimicrobial Agents  13
Emily L. Heil
Neha U. Sheth
William F. Wright

4. Introduction to Medical Microbiology  39
Nicole M. Parrish
Stefan Riedel

II. APPROACH TO FEVER AND LEUKOCYTOSIS

5. Fever of Unknown Origin  43
William F. Wright

6. Leukocytosis  51
William F. Wright

III. APPROACH TO BLOODSTREAM AND CARDIOVASCULAR INFECTIONS

7. Infective Endocarditis  57
Jennifer Husson
William F. Wright

8. Infectious Myocarditis  67
William F. Wright

9. Cardiovascular Implantable Prosthetic Device Infections  75
William F. Wright
10. Infections Involving Intravascular Catheters and Suppurative Thrombophlebitis 82
   Eric Cox
   Kerri A. Thom

IV. APPROACH TO PULMONARY INFECTIONS

11. Pneumonia 91
    Ulrike K. Buchwald
    Devang M. Patel

12. Empyema 103
    Gonzalo Luizaga
    Luciano Kapeluszynik
    William F. Wright

13. Lung Abscess 110
    Adrian Majid
    Ulrike K. Buchwald
    Devang M. Patel

14. Tuberculosis 116
    David W. Keckich
    Ulrike K. Buchwald

V. APPROACH TO GASTROINTESTINAL INFECTIONS

15. Diverticulitis 126
    William F. Wright

16. Appendicitis 133
    William F. Wright

17. Pancreatic Infections 140
    William F. Wright

18. Infectious Peritonitis 147
    William F. Wright

19. Infectious Diarrhea 155
    William F. Wright

20. Clostridium difficile Colitis 162
    Ryan S. Arnold
    William F. Wright

21. Infectious Gastritis—Helicobacter pylori 169
    William F. Wright

22. Anorectal Abscess and Fistula-in-Ano 176
    William F. Wright

VI. APPROACH TO HEPATOBILIARY INFECTIONS

23. Cholecystitis 181
    William F. Wright
24. Acute Cholangitis 187
William F. Wright

VII. APPROACH TO HEPATIC INFECTIONS
25. Hepatic Abscess 192
William F. Wright
26. Hepatitis A 198
William F. Wright
27. Hepatitis B 203
Luciano Kapeluszni
Robit Talwani
William F. Wright
28. Hepatitis C 209
Robit Talwani
Luciano Kapeluszni
William F. Wright

VIII. APPROACH TO RENAL–URINARY INFECTIONS
29. Urinary Tract Infections 220
Janaki C. Kuruppu
William F. Wright
30. Pyelonephritis and Renal Abscess 226
Jason Bailey
Janaki C. Kuruppu
William F. Wright
31. Catheter-Related Urinary Tract Infections 234
Clare Rock
Kerri A. Thom
William F. Wright

IX. APPROACH TO NEUROLOGICAL INFECTIONS
32. Meningitis and Ventriculitis 240
William F. Wright
33. Infectious Encephalitis 248
William F. Wright
34. Brain Abscess 254
William F. Wright

X. APPROACH TO ORTHOPEDIC-RELATED INFECTIONS
35. Osteomyelitis 261
William F. Wright
36. Mandibular and Maxillary Osteomyelitis 270
William F. Wright
### Approach to Skin and Soft-Tissue Infections

<table>
<thead>
<tr>
<th>Chapter</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>39.</td>
<td>Non-Necrotizing Skin and Soft-Tissue Infections</td>
<td>299</td>
</tr>
<tr>
<td>40.</td>
<td>Necrotizing Skin and Soft-Tissue Infections</td>
<td>307</td>
</tr>
<tr>
<td>41.</td>
<td>Diabetic Foot Infections</td>
<td>312</td>
</tr>
</tbody>
</table>

### Approach to Sexually Transmitted Infections

<table>
<thead>
<tr>
<th>Chapter</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>42.</td>
<td>Sexually Transmitted Diseases</td>
<td>320</td>
</tr>
<tr>
<td>43.</td>
<td>HIV and AIDS</td>
<td>333</td>
</tr>
</tbody>
</table>

### Approach to Infections Related to Obstetrics and Gynecology

<table>
<thead>
<tr>
<th>Chapter</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>44.</td>
<td>Obstetrics and Gynecology-Related Infections</td>
<td>359</td>
</tr>
</tbody>
</table>

### Approach to Eye Infections

<table>
<thead>
<tr>
<th>Chapter</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>45.</td>
<td>Infectious Keratitis</td>
<td>370</td>
</tr>
<tr>
<td>46.</td>
<td>Endophthalmitis</td>
<td>377</td>
</tr>
</tbody>
</table>

### Approach to Sepsis

<table>
<thead>
<tr>
<th>Chapter</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>47.</td>
<td>Sepsis and Septic Shock</td>
<td>384</td>
</tr>
</tbody>
</table>
XVI. APPROACH TO TRANSPLANT-RELATED INFECTIONS

48. Hematopoietic Stem Cell Transplant Infections 395
   Michael Tablang
   David J. Riedel

49. Solid-Organ Transplant Infections 401
   Michael Tablang
   Charles E. Davis

XVII. APPROACH TO ECTOPARASITE-RELATED INFECTIONS

50. Lyme Disease 409
    William F. Wright

XVIII. INFECTION CONTROL AND EPIDEMIOLOGY

51. Travel Medicine 416
    Susan L. DeBiase
    William F. Wright

52. Basic Approach to Infection Control and Epidemiology 436
    Clare Rock
    Surbhi Leekha

53. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2),
    Also Known as Coronavirus Disease 2019 443
    William F. Wright
    Jenny Townsend
    Erica N. Johnson

Index 449
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We have been gratified by the popularity of the first edition of The Essentials of Clinical Infectious Diseases. It has been more than five years since the first edition of this book presented readers with the essential aspects of the subspecialty infectious diseases. The popular reception of the book and the rapid expansion of medical knowledge call for a new edition to assist readers through this medical transformation—from a demystified wonder to a commonplace tool in medical education.

This edition (a) provides technical corrections, updates, and clarifications in all 45 chapters of the original book; (b) adds six new chapter topics; (c) includes new developments that are consistent with the published peer-reviewed medical literature, published relevant clinical practice guidelines, and updated bibliographical references at the end of each chapter; and (d) elucidates subtle issues that readers and reviewers have found perplexing, objectionable, or in need of elaboration.

Our main audience remains the students and medical providers in training. However, information within this book evolved from prior formal didactic lectures or bedside clinical teaching on clinical infectious diseases, microbiology, and antimicrobial pharmacology that was delivered to help students, residents, fellows, and primary care physicians. Current basic science and clinical concepts regarding each relevant infectious disease topic are still written as a synoptic account to make these topics clear and practical for the readers of this text. Teachers who have taught from this book before should find the revised edition more lucid and palatable. We continue to adhere wherever possible to a standard pattern of description that aims to define the topic; provide an introduction that would include classification, pathophysiology, and epidemiologic information; list relevant causative microorganisms; describe the clinical aspects and approach to the topic with the physical examination and relevant laboratory methods, diagnostic imaging, and appropriate antimicrobial therapy. This updated essentials text also includes new chapters that readers will hopefully find useful beyond the basic clinical syndromes: introduction to clinical reasoning and statistics, introduction to antimicrobial stewardship, and basic approach to travel medicine.

While medicine continues to evolve and the amount of knowledge a learner must retain may seem daunting, knowing basic concepts can make the approach to a patient with a possible infection an easy and exciting task. Although this text is arranged by certain infectious disease topics, patients typically present with a constellation of symptoms and signs. Knowing basic concepts, therefore, can help clinicians arrive at the diagnosis of the disease causing the patient’s symptoms and signs. This process (clinical problem solving) begins by a discussion with the patient of the chronology of events associated with the symptoms or signs experienced as well as asking appropriate relevant questions. Additionally, a complete physical examination is then performed for diagnostic clues that then lead to the formulation of the most appropriate differential diagnosis that is based on an understanding of these basic concepts. Based on the initial discussion and examination, appropriate laboratory or imaging tests are ordered to support or refute the diagnostic considerations. The goal of this text is to help guide
the reader through the diagnostic evaluation as well as the process of caring for the patient with an infection.

The editor and contributing authors have collaborated to prepare chapters consistent with the peer-reviewed published medical literature, published clinical practice guidelines and their teaching, clinical, and research activities. Each chapter concludes with important medical references that may also include reference to a “classic” article regarding the infectious disease topic that can be utilized by the reader as additional reading. Through this text the authors strive enthusiastically to impart to readers a solid fundamental knowledge and approach to clinical infectious diseases that will sustain them adequately in their chosen medical professional career.

William F. Wright, DO, MPH
I am very grateful to all the contributing authors for their hard work and dedication to this book and our profession. I would also like to personally thank several additional colleagues who reviewed many sections of the manuscript and/or provided many helpful suggestions. The book would not have been possible without the support and assistance of these additional individuals:

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INTRODUCTION AND BASICS OF CLINICAL REASONING

William F. Wright

I. INTRODUCTION. Akkadian cuneiform inscriptions from the 6th century BCE suggest that medicine of early Mesopotamian societies involved supernatural interpretations of disease with blaming of gods and ghosts frequently. Medical epistemology in Hellenistic Palestine and Greco-Roman societies from the 5th century BCE embodied the philosophical notion of both a macrocosm and microcosm. The writings of Aristotle, as well as early Greek philosophers such as Plato and Pythagoras, proposed the world, or macrocosm, was composed of the four elements of air, earth, fire, and water. This corresponded to a microcosm with the harmonious balance of four bodily elements (blood, phlegm, yellow bile, and black bile), which were known as humors. In his treatise, *On the Nature of Man*, Hippocrates introduced the classic theory of humors and their imbalances as a means of explaining disease. The Roman physician Galen endorsed this pathophysiology and further defined medicine for Medieval Western Europe. The classic theory of humors predominated medical thinking until the 19th century when both Louis Pasteur and Robert Koch provided proof of the microbial basis of disease. This ushered in the era of what would now be considered a rational scientific basis of medicine.

Modern clinical medicine and infectious diseases have dramatically changed over the past century. The practice has evolved from a healing art in which standards were based mainly on the personal experience of physicians to a discipline focused on the scientific method and evidence-based practice standards. While scientific advances serve as the evolutionary basis for the diagnostic and therapeutic approaches to common medical and infectious-disease conditions, reconciling the traditional physical diagnostic approach with contemporary diagnostic methods has been a continuous process throughout the history of medicine and clinical infectious diseases. The approach to the patient with an infectious disease is still best accomplished by a systematic method that combines the critically important comprehensive history and physical examination with the added benefits of contemporary technology. This process, the basis of the fundamental skills of medical diagnosis and treatment, strives to improve the physician's clinical reasoning and includes:

1. Understanding disease definitions, mechanisms, and patterns
2. Identifying the patient's chief complaint and performing a chronologically accurate medical history
3. Formulating a differential diagnosis based on the chief complaint and medical history (also known as the pretest probability)
4. Performing physical-examination maneuvers that will support or refute the conditions being considered in the differential diagnosis
5. Ordering appropriate diagnostic and laboratory tests and interpreting the results in relation to the differential diagnosis (also known as the posttest probability)

6. Implementing an appropriate evidence-based treatment plan

The purpose of this clinical reasoning is to establish a systematic and rational approach to medical decision making that allows the physician to explain the patient’s symptoms based on one unified diagnosis (i.e., Occam’s razor).

Critically important when applying this process to clinical infectious diseases are the chief complaint and an extended medical history that ideally includes antibiotic uses and allergies, past medical conditions and/or infections, sexual practices, drug use, travel destinations, occupational history, screening tests (e.g., purified protein derivative [PPD]), and vaccinations, which when taken together, provide important clues to the risk of acquiring an infection. However, one of the more difficult processes in clinical infectious diseases is the synthesis of all data including organisms identified in the microbiology laboratory to distinguish between an infectious process and colonization. Colonization is generally considered to be the presence of a particular microorganism or group of microorganisms (i.e., normal flora) in which their presence does not create a specific host immune response (i.e., infection). In contrast, infection is most commonly due to the invasion of body tissues with a particular microorganism or group of microorganisms, which elicits an immune response that results in a disease state.

II. EVIDENCE-BASED MEDICINE BASICS. A group of further categories highlighting important concepts regarding clinical reasoning and evidence-based medicine principles is listed in the following. These concepts should be kept in mind when evaluating all encountered patients, including infectious diseases, so as to provide a systematic and rational approach to the clinician’s medical decision making.

A. Basics of Clinical Reasoning

1. Differential diagnosis. The differential diagnosis is a systematic process for considering the most likely possible causes of a patient’s symptom or physical finding. This process begins with evaluating a hypothesis by matching the patient’s findings with the clinician’s internal understanding of disease. Most often an associative model of disease, also known as pattern recognition, is used that consists of clinical findings, illness progression, predisposing characteristics, and complications that are associated with a disease.

Clinical hypothesis generation begins with the patient’s chief complaint and a chronologic account of illness from its beginning. This approach provides valuable information and perspective on the patient’s illness. It also respects the patient in allowing time to recount the story as well as provide the clinician time to think, write down some diagnoses to consider, and observe the patient for diagnostic clues. Once the patient has provided a chronologic account of the illness the clinician should ask specific questions to test each of the initial diagnostic hypotheses (e.g., cross-examination history taking). The combined patient recounted and cross-examined history (e.g., chief complaint, history of present illness, and past medical–surgical history) should generate the most hypotheses. The physical examination is then usually the time to gather objective physical clues to rank, confirm, or discard a hypothesis. Remember that a pathognomonic finding usually improves diagnostic efficiency and establishes a diagnosis for one disease, but very few of these findings exist.
When the considered hypotheses have been ranked in order of plausibility, the clinician then has to decide whether to withhold any further testing or treatment, begin treatment without further testing, or gather more information with diagnostic testing prior to beginning treatment. The choice among these three alternatives is guided by probability and utility (e.g., benefit vs. harm).

2. Probability. Probability in medicine is referred to as either the present state of the patient or the possibility of a future patient event. Predictors of the present state of the patient would involve information from a cross-sectional design study. Predictors of a possible future event of the patient would involve information from a cohort design study.

a. Pretesting probability. Defined as the probability of a patient having the target disorder before a diagnostic test result is known. Mathematically, it can be calculated as the proportion of patients with the disorder divided by both those with and without the disorder expressed as a percentage.

\[
\text{Pretesting probability} = \frac{\text{Disease}}{\text{Disease} + \text{No disease}}
\]

b. Posttesting probability. Defined as the probability of a patient having the target disorder after a diagnostic test result is known. The clinician can calculate the posttesting probability of a disease using the Bayes theorem.

3. The Bayes theorem. Reverend Thomas Bayes (1702–1761), an English clergyman, developed a method of predicting probability that an event is true given that another event is true. This is referred to as the “notion of conditional probability.”

In medical terms, the Bayes theorem is the probability (P) of a medical hypothesis (H) conditional upon new information or evidence (E). It is expressed mathematically as:

\[
P(H|E) = \frac{P(E|H) \times P(H)}{P(E)}
\]

Another way of expressing this is as follows:

\[
P(H|E) = \frac{\text{Probability of the evidence given the hypothesis} \times \text{the probability of the hypothesis}}{\text{The probability of the evidence}}
\]

Therefore, using this theorem the clinician can calculate or estimate the probability of disease based upon the following: (a) pretesting probability of disease, (b) probability of a history of present illness finding and physical examination or laboratory test result conditional upon the patient having the disease (e.g., sensitivity), and (c) probability of a history of present illness finding and physical examination or laboratory test result conditional upon the patient not having the disease (e.g., specificity).

B. Incidence and Prevalence

Clinically relevant measures of the frequency of events are usually expressed as fractions in which the numerator is the number of patients experiencing the outcome (e.g., cases) and the denominator is the number of people in whom
the outcome could have occurred (e.g., population). The measure of disease is usually expressed as the following:

1. **Incidence.** This refers to the number of new cases of disease (numerator) occurring in a population at risk for disease (denominator) in a given time frame (e.g., weeks, months, or years). Incidence is a measure of rate of disease and estimates the risk of disease.

2. **Prevalence.** This refers to the number of people possessing the clinical condition, or disease (numerator), occurring in a given population of people (denominator). Prevalence is a measure of proportion and estimates the burden of disease. *Prevalence is also called pretesting probability, the probability of disease before the test result is known.*

C. **Sensitivity, Specificity, and Predictive Values**

1. **Sensitivity (Se).** Defined as the proportion of people with the disease who also have a positive test (e.g., history of present illness in question and/or physical examination or laboratory test) for the disease in question. A sensitive test is helpful to identify or rule in disease.

2. **Specificity (Sp).** Defined as the proportion of people without the disease who also have a negative test (e.g., history of present illness in question and/or physical examination or laboratory test) for the disease in question. A specific test is helpful to exclude or rule out disease.

3. **Positive predictive value (PPV).** The probability of disease in a patient with a positive test result for the disease in question. The more specific a test is, the better will be its PPV. As the prevalence of disease in a population approaches zero, the PPV of a test also approaches zero.

4. **Negative predictive value (NPV).** The probability of *not* having the disease in a patient with a negative test result for the disease in question. The more sensitive a test is, the better will be its NPV. As the prevalence of disease in a population approaches 100%, the NPV of a test approaches zero.

### SENSITIVITY AND SPECIFICITY 2×2 CONTINGENCY TABLE

<table>
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<th>Test Result</th>
<th>Disease</th>
<th>Disease Status</th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Present</td>
<td>Absent</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>A</td>
<td>B</td>
<td>PPV = A/A + B</td>
</tr>
<tr>
<td>Negative</td>
<td>C</td>
<td>D</td>
<td>NPV = D/C + D</td>
</tr>
</tbody>
</table>

C is also known as false negative.
B is also known as false positive.
Cutoff point for a test is the point on a continuum between a positive test and a negative test.

5. **Receiver operating characteristic (ROC) curve.** ROC analysis had its beginnings in observations made in Britain during World War II when radar receiver operators were being assessed on their ability to differentiate signal (e.g., enemy aircraft) from noise (e.g., flocks of birds). Its use in medicine to assess diagnostic test performance was first described by Lee B. Lusted, MD, in 1971.
In medicine, ROC is a measure of the distinguishing properties of a test for the disease in question. The curve is constructed by graphically plotting the true-positive rate (e.g., sensitivity) against the false-positive rate (e.g., 1 – specificity) over a range of possible test cutoff values. The best test cutoff value is a graphically plotted point on the scale that maximizes the sensitivity value and minimizes the false-positive rate. The overall accuracy of the test then can be described as the area under the curve (AUC).

In general, the AUC value and the quality of the test are interpreted as follows:

<table>
<thead>
<tr>
<th>AUC Value</th>
<th>Test Quality</th>
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<tbody>
<tr>
<td>0.9–1.0</td>
<td>Excellent</td>
</tr>
<tr>
<td>0.8–0.9</td>
<td>Good</td>
</tr>
<tr>
<td>0.7–0.8</td>
<td>Fair</td>
</tr>
<tr>
<td>0.6–0.7</td>
<td>Poor</td>
</tr>
<tr>
<td>0.5–0.6</td>
<td>Fail</td>
</tr>
</tbody>
</table>

D. Odds, Risk, and Likelihood Ratios

1. **Odds ratio (OR).** The OR is a measure of association between an exposure and an outcome. ORs are used to compare the relative odds of the occurrence of the outcome of interest (e.g., disease or disorder), given exposure to the variable of interest in **case-control studies**. The OR can also be used to determine whether a particular exposure is a risk factor for a particular outcome and to compare the magnitude of various risk factors for that outcome.

   In **case-control studies** researchers start with two cohorts of patients, one group with the outcome of interest (e.g., case group) and one group without the outcome of interest (e.g., control group). Then researchers look retrospectively for the given exposure.

   Mathematically the OR is expressed as:

   \[ \text{Odds ratio} = \frac{\text{odds of disease in exposed group}}{\text{odds of disease in unexposed group}}. \]

   In general, the values of OR are interpreted as:

   1. **OR = 1;** exposure does **not** affect odds of outcome
   2. **OR > 1;** exposure associated with higher odds of outcome
   3. **OR < 1;** exposure associated with lower odds of outcome

2. **Risk ratio or relative risk (RR).** The RR is a measure of the risk of a certain event happening in one group compared to the risk of the same event happening in another group. In a **cohort study** researchers start with two cohorts of patients, one group with the exposure and one group without the exposure (e.g., control group). Then researchers look prospectively for the outcome of interest. An RR value of 1 means there is no difference between the two groups in terms of their risk of disease, based on whether or not they were exposed to a certain substance or factor, or how they responded to two treatments being compared. An RR value greater than 1 or less than 1 usually means that being exposed to a certain substance or factor either increases
(RR greater than 1) or decreases (RR less than 1) the risk of disease, or that the treatments being compared do not have the same effects.

Mathematically these measures are expressed as:

Relative risk = risk of event (experimental group)/risk of event (control group)

Risk ratio = risk in exposed group/risk in unexposed group

### 3. Likelihood ratio (LR).

It is the likelihood that a given test result would be expected in a patient with the disease in question compared to the likelihood that the same result would be expected in a patient without the disease in question. LR values are used to assess the discriminating properties of a particular diagnostic test and to also assist in selecting an appropriate diagnostic test(s) or sequence of tests. These values have the advantage over sensitivity and specificity because they are less likely to change with the prevalence of the disorder.

Mathematically these measures are expressed as:

Positive LR [LR+] = sensitivity/(1 − specificity)

Negative LR [LR−] = (1 − sensitivity)/specificity

<table>
<thead>
<tr>
<th>Likelihood Ratio Value</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greater than 10</td>
<td>Strong evidence in support of diagnosis</td>
</tr>
<tr>
<td>5–10</td>
<td>Moderate evidence in support of diagnosis</td>
</tr>
<tr>
<td>2–5</td>
<td>Weak evidence in support of diagnosis</td>
</tr>
<tr>
<td>0.5–2</td>
<td>No clear evidence to support diagnosis</td>
</tr>
<tr>
<td>0.2–0.5</td>
<td>Weak evidence to refute the diagnosis</td>
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<tr>
<td>0.1–0.2</td>
<td>Moderate evidence to refute the diagnosis</td>
</tr>
<tr>
<td>Less than 0.1</td>
<td>Strong evidence to refute the diagnosis</td>
</tr>
</tbody>
</table>

### E. Testing and Treatment Thresholds

These thresholds describe levels of probability of disease at which one should be indifferent between ordering more testing and withholding more testing or giving treatment and withholding treatment. In other words, it is the relationship between the rational willingness of the physician to either perform more testing or treat and the probability of disease. The probability of disease at which one should be indifferent between testing, giving treatment, and withholding treatment is based primarily on maximizing the patient's welfare (e.g., benefits) and reducing the patient's potential harms of testing or treatment. While each clinical scenario is different, some general rules for applying this concept may be as follows:

1. The probability of disease at or above which the physician might be comfortable treating a patient with no further diagnostic testing is 80% (0.8).

2. The probability of disease at or below which the physician might be comfortable deferring further testing or treatment is 25% (0.25).

3. The probability of disease at or above which the physician might be comfortable deferring treatment in favor of requesting more diagnostic testing is 25% to 50% (0.25–0.5).
4. The probability of disease at or above which the physician might be comfortable starting treatment in conjunction with requesting further diagnostic testing is 50% to 80% (0.5–0.8).

F. Evaluating Published Data on Treatment
The accepted definition of a clinical trial is *any research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other controls) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.*
The recorded history of clinical trials begins with biblical descriptions in 500 BCE. While the evolution of clinical research traverses a long and fascinating journey, James Lind (1716–1794) is considered the first physician to have conducted a controlled clinical trial of the modern era while working as a surgeon on the British naval ship *Salisbury*. In his 1753 paper, *A Treatise on the Scurvy*, he details how he conducted a parallel arm medical experiment among scurvy afflicted seafarers. He discovered that lemons and oranges were most effective in treating the dreaded affliction. The first randomized control trial of streptomycin for treating pulmonary tuberculosis was carried out between 1946 and 1947 (published in 1948) by the Medical Research Council (MRC) of the United Kingdom (UK).

All clinical trials share basic common features:

1. **Basic structure**
   a. **Abstract.** This section presents an overview of the published article.
   b. **Introduction.** This section introduces the clinical topic with a review of previous relevant clinical trials and also states the primary and secondary research hypotheses.
   c. **Methods.** This section defines the patient population, lists the inclusion and exclusion criteria, describes the research design, defines the primary and secondary outcomes, and details the statistical methods and analysis.
   d. **Results.** This section summarizes the characteristics of each study group and describes the results of the study outcomes.
   e. **Discussion/conclusion.** This section provides an interpretation of the results in the context of previous studies, discusses the limitations and strengths of the study, and provides suggestions for future research.

2. **Phases of clinical trials.** Clinical trials are conducted in phases with each phase serving a particular purpose.
   a. **Phase I.** Initial testing of a new drug or treatment is performed on a small group of human subjects to evaluate a drug or treatment's safety, determine a certain safe dosage range, and identify side effects.
   b. **Phase II.** The new drug or treatment is tested on a larger group to determine its efficacy (e.g., whether it works under ideal circumstances).
   c. **Phase III.** Randomized controlled multicenter trials are performed on even larger patient groups to confirm effectiveness (e.g., whether the drug or therapy does more good than harm under usual care conditions).
   d. **Phase IV.** Postmarketing studies gather data on whether the drug affects population groups differently or whether there are side effects associated with its long-term use.
3. Questions to consider when evaluating a clinical trial

a. What are the study hypotheses, and are they clearly stated and relevant? The hypotheses of interest require a definition of dependent (outcome) and independent (treatment) variables. The primary hypothesis states the effect of an independent variable on a dependent variable. The secondary hypothesis states the effect of an independent variable on a dependent variable among specified subgroups.

b. Is the study population adequately described? Every trial should clearly state the inclusion and exclusion criteria, randomization procedure, and number of subjects in each group.

c. Are the observed differences due to chance (e.g., random error) or attributable to a true effect? Statistical testing involves an assessment of the probability of an observed difference in outcome when there is actually no true difference between groups (e.g., false-positive rate; p value). When the p value is less than .5 the difference is considered significant and due to a true effect. When the p value is greater than .5 the difference is not considered significant and due to chance or random error.

The probability of obtaining a significant result when a real difference exists is called the study power. A sample size large enough to achieve a power of 80% to 90% is desired.

d. Are the observed differences due to bias (e.g., systematic error)? The most common types of bias include subject selection, outcome measures, and confounding. Confounding is defined as the modification of the true relationship between the treatment and outcome. The greatest level of evidence in support of a true outcome difference is associated with randomized, controlled clinical trials, particularly in combination with other randomized trials in a systematic fashion (e.g., meta-analysis).

e. Are the observed differences modified by other factors? In general, inclusion of a variable in a multivariate model adjusts for confounding.

f. Are the observed differences relevant to the treatment of my patient? The aforementioned information represents a basic guide for the proper design and method of conducting a trial that readers of the medical literature should consider when evaluating the published results of a clinical trial and its potential clinical application to patient care.

This book is designed to assist physicians of any specialty and at all levels—students, residents, and attending—with the diagnosis and management of clinical infectious diseases. Within the book, we emphasize the core topics encountered by most physicians and highlight the definitions, classifications, microorganisms, clinical manifestations, physical-examination clues, contemporary diagnostic and laboratory methods, and treatment. A physician who utilizes the process outlined previously will ask the appropriate questions, elicit the pertinent symptoms and signs, order the appropriate diagnostic tests, and follow clinical reasoning to a definitive diagnosis and evidence-based treatment plan. In the end, this will result in optimal outcomes for patients and physicians alike.
BIBLIOGRAPHY
ANORECTAL ABSCESS AND FISTULA-IN-ANO

William F. Wright

I. INTRODUCTION

A. Definition. An anorectal abscess is a collection of pus in the area of the anus and rectum. An anorectal fistula (fistula-in-ano) is an abnormal communication between the anus and the perianal skin.

B. Epidemiology. The disease is more common in men (66%) when compared to women (34%). The majority of patients are between the ages of 21 and 40 years (66%).

C. Classification. The anatomic classification of anorectal fistula involves its relationship to sphincter muscles.

1. Intersphincteric fistula. Most common.
2. Transsphincteric.
4. Extrasphincteric. Least common.

Anal fistulas may also be classified as “simple” or “complex.” “Complex” anal fistulas include transsphincteric fistulas that involve greater than 30% of the external sphincter; suprasphincteric, extrasphincteric, and horseshoe fistulas; and anal fistulas associated with inflammatory bowel disease (IBD), radiation, malignancy, preexisting fecal incontinence, or chronic diarrhea. “Simple” anal fistulas have none of these complex features.

II. PATHOGENESIS

A. Cryptoglandular Theory. The most widely held theory concerning the cause of anorectal abscess and resultant fistula-in-ano disease is obstruction of anal glands and ducts. Anal glands and ducts discharge mucus in the area called the zone of transition (the transition of somatic skin extending halfway along the anal canal to the rectal portion of the colon) around the base of anal crypts. Enteric microorganisms entering the anal gland channel initiate acute inflammation and resultant gland obstruction with abscess formation. Once an abscess has formed, infected material will migrate through any channel (or sinus tract) to the exterior. Fistula-in-ano is virtually a sinus tract opening secondary to an infected anal gland, which opens through a minute ductal opening in an area of the anal crypt.
III. MICROBIOLOGY OF ANORECTAL ABSCESS

A. Aerobic and Anaerobic Bacteria (Cryptoglandular abscess). The microbiology is best illustrated as a polymicrobial environment. Most common isolated microorganisms include:

1. *Staphylococcus aureus* spp, *Streptococcus* spp, and *Enterococcus* spp
2. *Escherichia coli* and *Klebsiella pneumoniae*
3. *Finegoldia magna* (formerly *Peptostreptococcus* spp)
4. *Fusobacterium* spp
5. *Prevotella* spp
6. *Bacteroides fragilis* group spp
7. *Porphyromonas* spp
8. *Clostridium* spp

B. *Actinomyces* spp, particularly *Actinomyces israelii* and *Actinomyces meyeri*, most commonly are the result of foreign body penetration wound, trauma, or neoplastic disease. Risk factors include diabetes mellitus and HIV infection.

C. Lymphogranuloma venereum (LGV) is usually associated as a sexually transmitted infection that can manifest as either a unilateral inguinal syndrome (e.g., painful inguinal lymphadenopathy) or anorectal syndrome characterized best as hemorrhagic proctocolitis. Unlike other *Chlamydia trachomatis* related infections, LGV serovars L1, L2, and L3 are associated with inflammatory lesions of lymphatic tissue. Most cases of anorectal syndrome involve serovar L2b and occur in men who have sex with men (MSM), particularly unprotected anal receptive intercourse.

D. Mycobacterial Infections include predominantly *Mycobacterium tuberculosis* as a result of pulmonary tuberculosis, supporting the most common mechanism of anorectal abscess as gastrointestinal tract ingestion of a large number of microorganisms.

E. Fungal Pathogens include rarely *Candida* species.

IV. CLINICAL MANIFESTATIONS OF ANORECTAL ABSCESS

A. Pain (100% of patients), perianal swelling (96% of patients), and fever (19% of patients) are considered the hallmarks associated with anorectal abscess.

B. Additional symptoms may include: gluteal pain, rectal bleeding, dysuria, and urinary retention.

V. APPROACH TO THE PATIENT

A. History. A complete and chronologically accurate history should be obtained in all suspected cases of anorectal abscess. The history should focus on the timing of events, risk factors, comorbid conditions, medication allergies, recent infections, and recent antimicrobial therapy. An anorectal abscess should be included in the differential diagnosis of any patient who presents with anorectal pain, swelling, and fever.

Crohn disease, obstetric trauma, or local irradiation can increase the risk of developing anorectal fistulas. Other comorbid conditions associated
with anorectal abscess and fistula-in-ano disease include ulcerative colitis, episiotomy, prostatectomy, anorectal carcinoma, hematologic malignancy, and penetrating foreign body injury.

**B. Physical Examination.** A complete physical examination should be performed, but areas of focus include:

1. **Vital signs.** Fever is common; however, patients may or may not demonstrate tachypnea.

2. **Anorectal examination.** On physical examination, there may be spontaneous or digitally expressed discharge, an open sinus, granulation tissue, or a palpable cord. If the patient cannot tolerate a digital examination, anesthesia is needed. Goodsall and Miles’s so-called *rule* states that fistulas with an external opening lying above a horizontal line drawn through the center of the anal canal, with the patient in the lithotomy position, usually drain directly into the anal canal. Fistulas lying below this horizontal line usually drain into the midline posteriorly. The predictive accuracy of this rule is 40% to 90% for posterior fistulas and 50% to 70% for anterior fistulas.

3. **Genitourinary examination.** Anorectal abscesses can be associated with sexually transmitted diseases (STDs) such as LGV (see the preceding), syphilis, gonorrhea, and chlamydia infection.

4. **Pulmonary examination.** Anorectal abscesses can be associated with pulmonary tuberculosis.

**C. Laboratory Studies**

1. **Complete blood count (CBC).** Routinely ordered and may reveal leukocytosis, leukopenia, and anemia of chronic disease.

2. **Basic metabolic panel (BMP).** Routinely ordered but nonspecific for anorectal abscess infections.

3. **Blood cultures.** Commonly two sets are ordered but are of low yield.

4. **Serum rapid plasma reagin (RPR) and urine for gonorrhea and chlamydia infection.** Should be obtained in patients with immunosuppressed conditions (e.g., HIV) or epidemiologically associated risk factors.

5. **Deep tissue sample for Gram stain and routine cultures** are more likely to yield results beneficial to guide further antimicrobial therapy in complicated disease (e.g., peritoneal abscess, secondary peritonitis, necrotizing skin and soft-tissue infection, and/or inflammatory bowel disease); however, superficial swab cultures from ulcer or sinus tracts may not identify the true bacteriologic pathogen because of bacterial colonization of wound surfaces with microorganisms typically not considered pathogenic (e.g., *Enterococcus* and/or coagulase-negative *Staphylococcus* spp).

**D. Radiologic Studies.** Superficial abscesses and simple fistulas, in general, do not require diagnostic imaging.

1. **Endoanal ultrasound (EUS) and transperineal ultrasound (TPUS).** EUS is an imaging study performed in two or three dimensions, with or without peroxide enhancement, and it typically identifies an abscess and fistula-in-ano in 73% to 100% of the cases. TPUS is a noninvasive alternative to EUS with an estimated sensitivity of 85%.
2. **Abdominal and pelvic CT or MRI.** More useful for identifying smaller abscesses, recurrent fistula-in-ano, and perianal Crohn disease. The sensitivity of CT was 77% and 70% in immunocompetent and immunocompromised patients. An advantage of MRI over CT is better identification of both anorectal abscess and associated fistula tracts. MRI has an overall sensitivity of 82% to 90% for the identification of abscesses and fistula-in-ano.

3. **Fistulography.** A contrast-based injection study of the fistula under fluoroscopy may also be an effective means of studying an anal fistula.

VI. MANAGEMENT OF ANORECTAL ABSCESS

A. **Medical Management.** Appropriate antimicrobial therapy with routine incision and drainage of an uncomplicated anorectal abscess in healthy patients does not improve healing or reduce recurrence; therefore, it is not generally recommended. Selective use of antibiotics for patients with anorectal abscess complicated by cellulitis, systemic inflammation, leukocytosis, leukopenia, or immunosuppression (e.g., HIV, use of immunosuppressive therapy, prolonged use of corticosteroids, or absolute neutrophil count [ANC] less than 1000/mm³) has been advocated. General antimicrobial therapy recommendations for the treatment of anorectal abscesses include (dosing assumes normal renal function):

1. **Cryptoglandular type abscess.**
   
   a. Immunocompetent patient. Metronidazole 15 to 20 mg/kg orally divided into 3 or 4 doses daily with or without ciprofloxacin 500 mg once or twice daily for a duration of 5 to 10 days.

   b. Immunocompromised patient. Metronidazole 15 to 20 mg/kg orally divided into 3 or 4 doses daily with or without ciprofloxacin 500 mg once or twice daily for a duration of 2 to 4 weeks.

   c. Patients with Crohn disease. Metronidazole 15 to 20 mg/kg orally divided into 3 or 4 doses daily with or without ciprofloxacin 500 mg once or twice daily for a duration of 8 to 10 weeks.

2. **Mycobacterium tuberculosis type abscess.** The standard therapy is the 6-month antimicrobial course that is the same as for active pulmonary tuberculosis, which includes oral isoniazid 5 mg/kg daily, rifampin 10 mg/kg daily, pyrazinamide 20 to 25 mg/kg daily, and ethambutol 15 to 20 mg/kg daily.

3. **Actinomyces type abscess.** Penicillin G 10 to 20 million units intravenously divided four times daily followed by oral penicillin V 2 to 4 g divided four times daily for a duration of 2 weeks to 6 months. Oral doxycycline 100 mg twice daily is an alternative for patients with documented penicillin allergy.

4. **LGV type abscess.** Oral doxycycline 100 mg twice daily for a duration of 21 days.

B. **Surgical Management.** The primary treatment of anorectal abscess remains surgical drainage. In general, the incision should be kept as close as possible to the anal verge to minimize the length of a potential fistula, while still providing adequate drainage. Packing the wound has demonstrated equivalent or superior abscess resolution, with less pain and faster healing when compared to patients whose wounds are left unpacked.

The primary goal of operative treatment of anal fistula-in-ano is to obliterate the internal fistulous opening and any associated epithelialized tracks and to
preserve anal sphincter function. Simple fistula-in-ano in patients with normal anal sphincter function may be treated with fistulotomy. In a fistulotomy the surgeon first probes to find the fistula's internal opening. Then the tract is cut open and scraped followed by having its contents flushed out. Then its sides are stitched to the sides of the incision in order to lay open the fistula. A more complicated fistula, such as a horseshoe fistula (where the tract extends around both sides of the body and has external openings on both sides of the anus), is treated by usually laying open just the segment where the tracts join and the remainder of the tracts are removed.

*Marsupialization* of the wound edges after fistulotomy has been associated with less postoperative bleeding and accelerated wound healing and may also reduce the need for postoperative analgesics. It is a surgical technique of cutting a slit into an abscess or cyst and suturing the edges of the slit to form a continuous surface from the exterior surface to the interior surface of the cyst or abscess. Sutured in this fashion, the site remains open and can drain freely.

*Endoanal advancement flap* is a sphincter-sparing technique that consists of curettage of the fistula tract, suture closure of the internal opening, and mobilization of a segment of proximal healthy anorectal mucosa, submucosa, and muscle to cover the site.

With complex anal fistulas, initial seton placement (a silk string or rubber band) to control infection is typically followed by a secondary, definitive procedure to eradicate the fistula. A seton (silk string or rubber band) is used to either create scar tissue around part of the sphincter muscle before cutting it with a knife or allow the seton to slowly cut all the way through the muscle over the course of several weeks. The seton may also aid in the drainage of the fistula.

**VII. PROGNOSIS**

A. Inadequate drainage, loculations, horseshoe-type abscess, and failure to perform primary fistulotomy have been identified as risk factors for recurrent anorectal abscess.

B. Factors associated with failed surgical fistula repair include prior radiation, underlying Crohn disease, active proctitis, rectovaginal fistula, malignancy, obesity, and the number of previously attempted fistula-in-ano repairs.

**BIBLIOGRAPHY**
