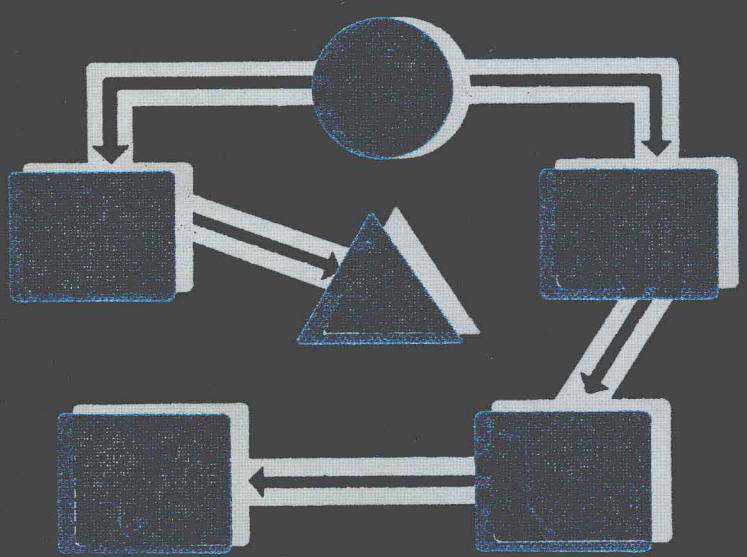
REILLY

PRACTICAL STRATEGIES IN OUTPATIENT MEDICINE

SECOND EDITION



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PRACTICAL STRATEGIES IN OUTPATIENT MEDICINE

SECOND EDITION

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PREFACE TO THE SECOND EDITION

The warm reception given the first edition of this book has been gratifying, but good reviews and satisfied readers don't necessarily warrant a second edition. This book was written to help fill a need. When it was first conceived in 1980, I was a clinician-teacher at Dartmouth, intrigued by the fun and complexity of ambulatory medicine yet frustrated by the dearth of literature useful to practitioners like myself and to the residents and students who considered following in our footsteps. Now, six years after the initial publication of *Practical Strategies in Outpatient Medicine,* several fine books and a few good journals address many of the concerns of primary care practitioners. Therefore, is the second edition of this book—updated, expanded and, I hope, improved—redundant? Does it still fill an unmet need?

Textbooks of ambulatory medicine tend to fall into one of two broad categories: the comprehensive tome or the quick-reference synopsis. The latter offers accessible advice about many disparate problems—an essential resource for the busy generalist clinician—but inevitably eschews depth for breadth of coverage. The former tries to combine breadth and depth—an awesome task (there really *is* a lot to learn to become a self-respecting generalist)—but the impact of such big books can be more inspirational than practical. These weighty compendia of information do serve as invaluable references; they help, in fact, to define the "specialty" of the generalist, an admirable accomplishment. But do traditional texts change physician behavior? Do they "teach" in the fullest sense? That is, do they both impart knowledge *and* "show how"?

My view is that no single book can do that for the vast field of general medicine. If one could, none of us would have the time to read it—let alone write it and rewrite it before it fell out of date. My guess is that electronic data bases soon will supersede the current generation of giant medical tomes. But computers have a long way to go—and limbs to grow—before they can begin to convey a "hands-on" approach to clinical medicine. This book, whatever its limitations in scope or style or quality, tries to do just that.

The bibliography to this new edition contains over 2000 more literature citations than the first edition—testimony not only to the expanded scope of the book but also to the vitality of recent clinical scholarship pertinent to ambulatory medical practice. Ironically, the overdue arrival of primary care disciplines as vibrant academic specialties has been accompanied by a diminishing interest in clinical primary care practice among American medical students. The causes of this disturbing trend (and the potential means to reverse it) are many. Some argue that the generalist who "knows it all" is a dinosaur; that the practice of sophisticated primary care medicine is hopelessly quixotic; and that the art of medicine will never again keep pace with the science. This book argues *Not so.* Nevertheless, the unsettling seeds of truth in each of these perceptions will grow into self-fulfilling prophecies if generalists continue to define themselves within the boundaries currently drawn by non-primary care specialists and ridiculous reimbursement rules. The mistaken notion that primary care involves only longitudinal health maintenance, episodic management of minor illness, and triage of "real disease" to multiple subspecialists lies at the heart of the primary care "image problem." This book was written with a very different agenda in mind: to teach the clinician *in detail* how to think about and how to approach in a practical way many undifferentiated clinical problems—and how to respond as evaluation and treatment *by the primary care physician* evolve over time.

Thus, each chapter in this book addresses a series of problems that often occupy several separate chapters in other books. This sometimes makes a chapter very long, and thus a brief synopsis (the "Contents Summary")* begins each chapter to highlight important information and to provide easier access to contents. But this is a deliberate design intended to put in perspective the diagnostic and treatment strategies that specifically challenge primary care clinicians. Tunnel vision, a relatively benign affliction when it strikes subspecialists, is profoundly disabling to the primary care practitioner and his or her patients. Overview—the "big picture"—is crucial when people, not diseases or syndromes, are our focus.

No doubt, some readers will object or misunderstand. For example, lists of differential diagnoses in this book are often lengthy and include both common and uncommon causes of the problem at hand. Some may feel that such detail is unnecessary, even pretentious. But I think the generalist should know a lot about what's common but also more than a little about what's not. In addition, the history and physical examination receive very detailed attention in every chapter of this book. Some may deem these matters too "basic." My view is that they are indeed so basic that they deserve much greater emphasis in both clinical textbooks and clinical research. (After all, these constitute the prior probability of disease, without which diagnostic tests will be misguided or misunderstood.) Finally, diagnostic hypotheses are formulated and tested in this book both qualitatively and quantitatively. Time-tested clinical axioms, e.g., those about quacking ducks and zebras' hoofbeats, are explicated, whenever possible, by popular statistical and epidemiologic concepts. In this regard, likelihood ratios receive more ink than predictive values, but the financial cost,† probabilistic "yield," and potential misuse of tests receive the most.

Data from original clinical research studies are reproduced in much greater detail here than in the first edition. Your interpretation of these data may differ from my own or from the original authors'—one reason to reproduce the original data for your consideration. These studies occupy a prominent place in the book primarily to support or balance my own (sometimes rather dogmatic) conclusions. It is my hope that more than a few readers will be stimulated to investigate some

*At the conclusion of each chapter, a series of "Illustrative Cases" is followed by "Illustrative Case Discussions," whose intent is to focus selected chapter material by applying it to actual patients from my own clinical practice. One suggested shortcut when approaching different chapters is to read the Contents Summary at the beginning of the chapter and the Illustrative Cases (as "unknowns") at the end; if you are not surprised or interested by what you read there, chances are that you know (or don't want to know) most of the material in that chapter. If so, move on to another chapter.

†Unless otherwise specified, these represent actual costs of tests (including both technical and professional fees) in 1989–1990 at the Dartmouth-Hitchcock Medical Center. In general, drug costs listed in the book represent average *wholesale* prices, derived primarily from the 1989 *Drug Red Book.*

of these issues further. The need is substantial, the opportunity rich. With this in mind, a brief list of "Questions for Clinical Research" has been appended to each chapter. Those I have listed refer only to a few of the obvious, yet unanswered *practical strategic* questions raised during the course of each chapter. Others can formulate far better than I the many more fundamental scientific questions that cry out for answers.

Finally, formal quantitative decision analyses do not appear in this book. Although the complex interplay among clinical uncertainty, cost, urgency and patients' utilities is an important theme through the book, I remain ambivalent about "bedside" decision analysis as a routinely practical clinical tool. I hope that further work in this area will show that my skepticism is unfounded—*if only we could* quantitate patients' values in a clinically meaningful way. The collaboration of practitioners and researchers in "outcomes research" will point the way. Perhaps, in some small measure, this book will help.

BRENDAN M. REILLY

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The transition from single-authored to multi-authored textbook has not been an easy one, least of all for the expert contributors who have had to endure the intrusions and idiosyncrasies of an overprotective author-turned-editor. Each contributing author has been uncommonly gracious, punctual and dedicated—a very rare good fortune for an editor—and I thank them all for their fine work, patience, and understanding.

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Pierre Bastianelli and his staff painstakingly reproduced so many x-rays and photographs so well that the book would not be the same without their contribution.

Many of Bruce Farrell's fine drawings remain from the first edition, and now Sherry Manheimer's wonderful artistic talent is also evident throughout this book. What you can't see is her willingness to help, even when inconvenient for her, and her ever-smiling face no matter what vague craziness I asked her to draw perfectly and in record time.

Dave Kilmer, Carol Robins, Linda R. Turner, and John Dyson at Saunders have shown me again that a book's writer is but one member of a team. I feel fortunate to have been a member of theirs.

As with some other creations, the conceiving of a book is a lot more fun than its long gestation. Inevitably, and much too often, its nurturing steals attention from family and friends. My children, Brendan and Caitlin, are no strangers to the games of sibling rivalry, but it's just no fun to fight back when the "new kid" not only is insufferably demanding and passive-aggressive but also monopolizes the Macintosh day and night. Caitie and BJ will be as glad to see this thing finally done as I will be to see more of them. Finally, my wife Janice attends so lovingly and well to them and all our needs, despite the demands of her own very busy career, that any words here to "acknowledge" her will be trivial. Even when we are apart, she is with us, part of us and all we do. And that is all that matters.

BRENDAN M. REILLY

CONTENTS

1 SORE THROAT

CONTENTS SUMMARY

Infectious pharyngitis is the cause of most cases of *acute sore throat* in adults. Occasionally, the history will suggest systemic illness or throat pain referred from the head, neck, or mediastinum (see Table 1–2, p. 2), but local disorders of the mouth and pharynx are much more common and usually obvious. Diseases primarily affecting oral mucosa may involve the pharynx—herpes simplex or Coxsackie virus, aphthous stomatitis, candidiasis, and gingival infections—and their gross appearance often allows rapid diagnosis (see pp. 2–4). Among adolescents with sore throat, infectious mononucleosis must be considered especially if fever and pharyngitis are prolonged or if the patient has prominent posterior cervical lymphadenopathy (see Table 1–3 and pp. 4–5). In most patients with acute sore throat, however, the diagnosis or exclusion of streptococcal pharyngitis is the clinician's major task. (The appendix on p. 24 briefly presents the rationale for this effort.)

Although prevalence varies in different clinical settings (see Table 1–6, p. 7), only a small minority (5 to 25 per cent) of adult sore throats are streptococcal. Physical findings are both insensitive and nonspecific: very few patients have "classic findings"—fever, pharyngeal exudate, *and* tender adenopathy—and even among these, throat cultures grow group A streptococci in no more than half (see Table 1–4, p. 6). Such clinical findings are useful, however, for estimating the prior probability of streptococcal infection so that antibody tests and throat cultures can be used efficiently when making decisions about diagnosis and treatment. Figure 1–6 (see p. 10) indicates that some patients should be treated for presumed streptococcal infection without any tests but that most can be screened with rapid antibody tests, whose results will then determine the need for treatment and/or performance of throat cultures. Such an approach depends critically not only on the sensitivity and specificity of the antibody test used—these may vary greatly—but also on the clinical assessment of the patient's prior probability of streptococcal infection (see Table 1–7, pp. 8–9).

Ten days of oral penicillin (or erythromycin), 250 mg four times daily, or one intramuscular injection of 1.2 million units of benzathine penicillin is the recommended treatment for suspected or proven group A streptococcal pharyngitis (see pp. 9–12). Non–group A streptococci, chlamydiae, and mycoplasmas have been implicated as possible common causes of infectious pharyngitis (see Table 1–9, p. 11), but their role in causing sporadic endemic infections is controversial and their treatment is of unknown efficacy.

Only rarely is the patient with sore throat seriously ill; however, epiglottitis (see pp. 13–15), peritonsillar abscess (see p. 13), retropharyngeal abscess (see p. 16), diphtheria (see pp. 15–16), and pharyngeal or submandibular cellulitis (see pp. 16–19) can cause "complicated" (even life-threatening) sore throat. *Trismus, respiratory distress, difficulty swallowing even one's own saliva, and systemic toxicity (high fever, prostration)* are the usual clues to these infections, but their early presentation may be subtle. Laryngoscopy, neck radiographs, immediate ear-nose-throat (ENT) consultation, and/or hospitalization may be needed in such cases (see pp. 12–20). Delay in diagnosing early upper airway obstruction may prove fatal.

Figure 1–19 (see p. 21) summarizes the general approach to patients with acute sore throat.

Figure 1–13 (see p. 17) illustrates the approach to the patient with suspected "complicated" sore throat.

Chronic or recurrent sore throat can be a frustrating and difficult problem (see pp. 20–23). In adolescents, recurrent bacterial tonsillitis and protracted bouts of infectious mononucleosis are not rare and can usually be diagnosed by careful physical examination. (Tonsillectomy is an option for patients with documented recurrent tonsillar infections, especially if associated with symptoms of upper airway compromise; however, surgery is usually a last resort.) Subacute thyroiditis, reflux esophagitis, and cardiac disease are occasional (and treatable) causes of recurrent "sore throat," but postnasal drip, pharyngeal irritants, and somatization are probably much more common.

AN OVERVIEW

Phil, a 22-year-old man, comes to the clinic complaining of sore throat. For the past 2 days, he has noted painful swallowing with discomfort bilaterally in the posterior pharynx and under the angles of the jaw. He believes he has been febrile, but has not taken his temperature, and has noted no cough, rhinorrhea, or myalgias. He says that his roommate has had an undiagnosed sore throat for 6 days that seems to be getting better without treatment. There is no past history of acute rheumatic fever or diabetes mellitus.

The practical clinical approach to the patient with sore throat is usually straightforward and simple. Most such patients have nonstreptococcal pharyngitis that usually resolves in several days without specific treatment. A properly obtained throat culture (or group A "strep" antibody test) distinguishes these patients from the minority with streptococcal pharyngitis who do require specific antibiotic therapy. Most often, then, clinical decisions regarding whether, when, and how to treat the patient with sore throat are based on the results of these tests. Thus, many clinicians perform an antibody test or obtain a throat culture from all patients complaining of sore throat and prescribe antibiotics accordingly. Before accepting this "cookbook approach," however, a few generalizations should be remembered:

1. *Sore throat is not always synonymous with pharyngitis.* The patient with pharyngitis usually describes bilateral internal discomfort in the posterior pharynx, often associated with painful swallowing. Physical examination of the mouth and pharynx usually reveals erythema of the posterior pharynx with or without other findings that sometimes suggest a more specific diagnosis. When this is the case, infectious pharyngitis

is usually the problem. The differential diagnosis of infectious pharyngitis can be extensive (Table 1–1), but in fact very few of the common causes require specific treatment. *When the patient's description of "sore throat" is atypical of pharyngitis, and especially when examination of the pharynx is also completely normal, other causes of sore throat must be remembered.* Table 1–2 illustrates examples of systemic, mediastinal, and "head and neck" diseases that may cause the patient to complain of sore throat that is, in various ways, atypical of pharyngitis.

Sudden, very severe throat pain in a patient whose pharynx is normal on examination should recall the possibility of myocardial infarction, aortic dissection, pneumomediastinum, esophageal rupture, or mediastinitis. These patients are usually obviously ill. Recurrent episodes of *brief throat pain* may be due to angina pectoris, esophageal spasm, reflux esophagitis, glossopharyngeal neuralgia, or subacute thyroiditis. *Various systemic illnesses* may begin with prominent sore throat—juvenile rheumatoid arthritis in adults,[1] viral hepatitis, temporal arteritis, and others.

Careful examination of the head and neck (Fig. 1–1*A*) is always important, since otitis, sinusitis, salivary gland or thyroid inflammation,[2] dental problems, strains of the neck muscles, carotidynia,[3, 4] and some rare but life-threatening upper airway infections (for example, epiglottitis, retropharyngeal abscess—see below) will usually be thus suspected.

2. *Visualization of the mouth and pharynx (Fig. 1–1B) sometimes reveals physical findings that are diagnostic of a specific disease.*[5, 6]

Vincent's angina (necrotizing ulcerative gingivostomatitis) (Fig. 1–2) refers to infection with (usually) *Fusobacterium nucleatum* or *Borrelia vincentii* that begins as a characteristic gingivitis—the papillary gingivae are flattened and inflamed with typical gingival ulcerations, often covered with a fetid, grayish slough. The infection usually spreads to involve the oral mucosa or posterior pharynx with similar ulcerations. Fever, localized lymphadenitis, foul breath, and tonsillitis commonly coexist. Mouthwashes and broad-spectrum antibiotics (tetracycline or penicillin), followed by continuing dental and periodontal care, will be curative.

Primary herpes simplex infection (Fig. 1–3) is usually characterized by fever, headache, sore throat, and regional lymphadenopathy. The gingivae become inflamed, and yellowish vesicles soon develop, often involving the "attached" oral mucosa (palate, pharynx, gingiva) more than "unattached" mucosa (buccal mucosa, tongue). Several days later, the vesicles rupture to produce painful ulcerations in those same locations, which then usually heal spontaneously within 1 to 2 weeks. Secondary (recurrent) herpes simplex infection is usually a briefer version of the primary attack (healing within 7 to 10 days) in which the vesicles are usually small and grouped in clusters. Topical or oral acyclovir is often used today to treat these lesions, but its efficacy is uncertain in this type of herpes infection. Rarely, early lesions will be confined to one or both tonsils and may thus be confused with streptococcal tonsillitis or even a peritonsillar abscess (when unilateral).

Herpangina is a confusing name given to Coxsackie (not herpes) infections of the pharynx and oral mucosa. This diagnosis is usually suggested by multiple small ulcerations of the soft palate and pharynx. It may be difficult to distinguish primary herpes simplex infection from herpangina because the latter lesions are also often widespread and associated with "viral" symptoms (fever, headache, adenopathy), but herpangina usually occurs in sporadic outbreaks during the summer months and often is much briefer in duration (several days) than is primary herpes simplex infection (weeks).

TABLE 1–1. Causes of Infectious Pharyngitis

Common	Uncommon
Group A beta-hemolytic streptococci*	Herpes simplex
Non–group A beta-hemolytic streptococci†	Coxsackie virus
Chlamydia trachomatis	Anaerobic (Vincent's)*
Mycoplasma pneumoniae	*Candida albicans**
Epstein-Barr virus	Aphthous disease‡
Influenza	Cytomegalovirus
Parainfluenza	Rhinovirus
Adenovirus	Coronavirus
	*Neisseria gonorrhoeae**
	Enterovirus
	Reovirus
	Rubella
	Varicella

Rare

*Corynebacterium diphtheriae**
*Francisella tularensis**
Treponema pallidum (syphilis)*
*Mycobacterium tuberculosis**
*Haemophilus influenzae**
*Toxoplasma gondii**
Histoplasmosis*
Cryptococcosis
Staphylococcus aureus
Measles
Lyme disease*[171]
Yersinia enterocolitica
Corynebacterium hemolyticum

*Specific treatment available *and* necessary.
†B, C, F, and G group streptococci have been implicated.
‡Presumed but not proven to be infectious.
See also Shrestha M, et al: Am J Med 78:235–240, 1985.

TABLE 1–2. Sore Throat: Other Causes

Head and Neck Disorders	Systemic Diseases	Mediastinal Disorders
Otitis	Viral hepatitis	Myocardial infarction
Sinusitis	Juvenile rheumatoid arthritis	Aortic dissection
Salivary gland infection	Rubella	Pneumomediastinum
Dental infection	Poliomyelitis	Mediastinitis
Thyroiditis	Campylobacter enteritis	Esophageal rupture
Carotidynia	Mycoplasma pneumonia	Angina pectoris
Neck muscle strain	Acute leukemia	Esophagitis
Glossopharyngeal neuralgia	Toxic shock syndrome	Esophageal spasm
Retropharyngeal abscess	Temporal arteritis	Jugular/subclavian thrombophlebitis
Epiglottitis	Agranulocytosis	Aortitis
Trauma	Acquired immunodeficiency syndrome (AIDS)	
Allergy		
Foreign body		
Neoplasm		

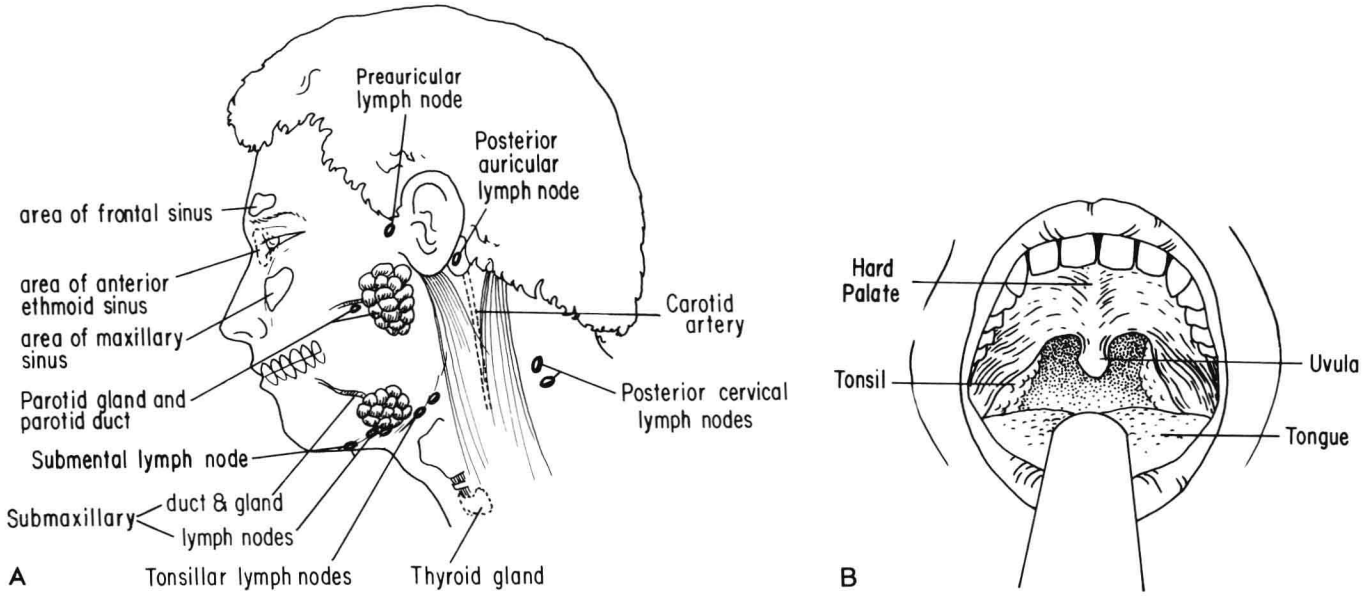


FIGURE 1–1. ***A*, Normal structures of the head and neck.** ***B*, Normal structures of the mouth and pharynx.**

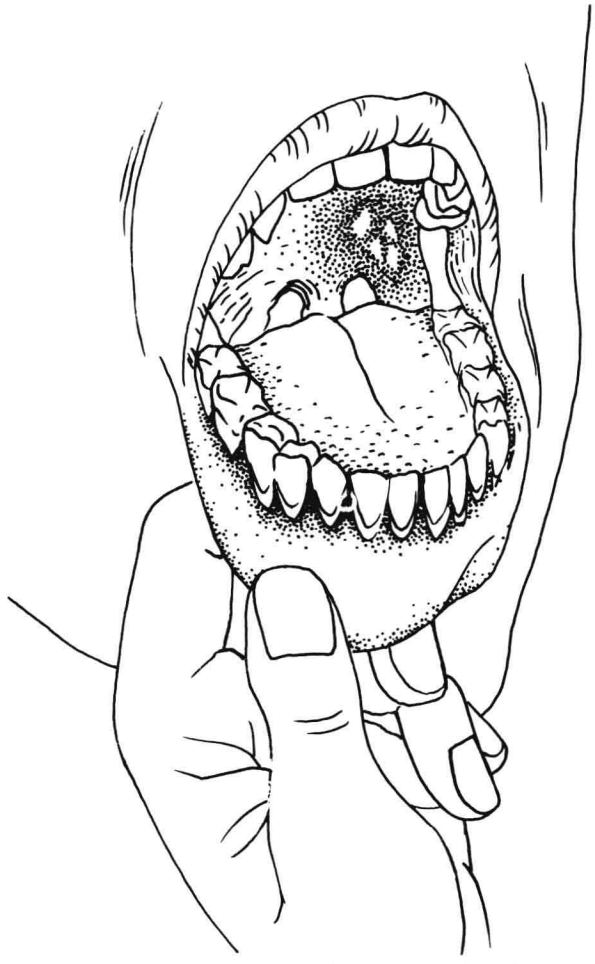


FIGURE 1–2. ***Vincent's angina*. The lower lip is pulled down to reveal that the gingivae of the lower teeth are swollen, inflamed, and covered with a gray slough. The buccal mucosa and posterior pharynx are also involved.**

Hand-foot-and-mouth disease, also caused by the Coxsackie virus, presents with similar oral lesions but is more aptly named because simultaneous lesions are found on the the palms and soles. No treatment is necessary.

Aphthous stomatitis ("canker sores") (Fig. 1–4) may be confused with herpes, Coxsackie, or other viral causes of gingivostomatitis, but it usually presents as discrete, shallow ulcerations (without preceding vesicles) localized to the "unattached" oral mucosa (inner lip, buccal mucosa, tongue). The

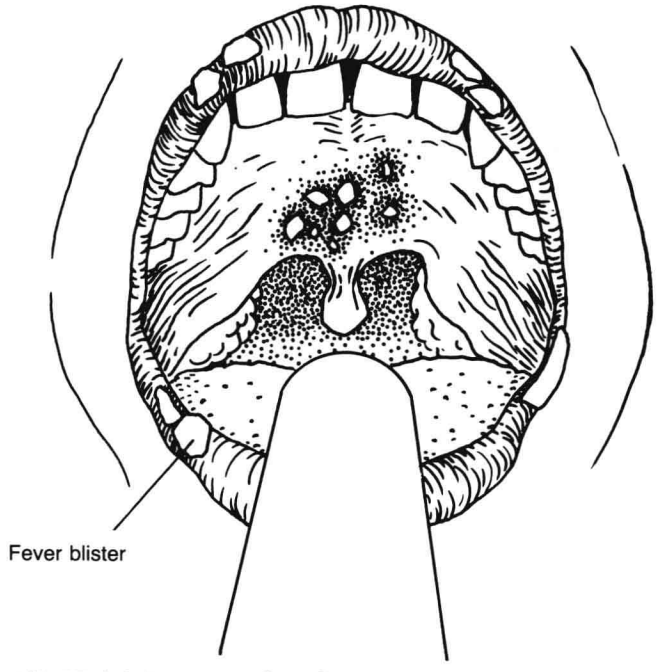


FIGURE 1–3. ***Herpes simplex infection*. The grouped, inflamed vesicles and superficial ulcerations on the palate are typical.** ***Herpangina*** **(Coxsackie) will have a similar appearance, but lesions are usually more widespread and the "cold sore" is less apparent.**

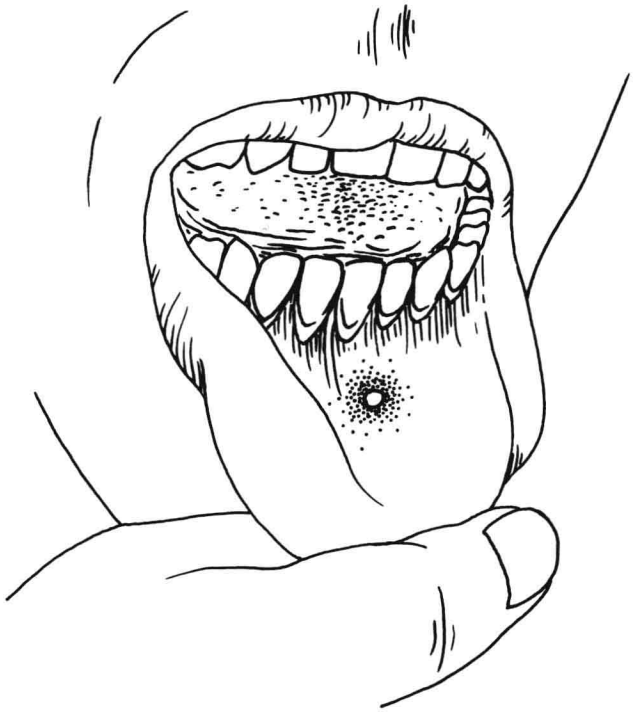


FIGURE 1–4. Aphthous stomatitis ("canker sore").

lesions are usually very tender, may vary in size and duration (some authorities thus distinguish minor and major aphthous lesions[7, 8]), and frequently recur. (Minor aphthous lesions—by far the most common—usually persist for 7 to 14 days.) The etiology is unknown.

Treatment of viral or aphthous stomatitis is largely symptomatic. When painful lesions are few and well localized, as is usually the case with aphthous stomatitis, topical steroids or anesthetics in a hydrocortisone acetate (Orabase) vehicle (for example, triamcinolone acetonide [Kenalog] or Benzocaine in Orabase) will often be soothing. More widespread eruptions are sometimes treated with tetracycline suspensions (the contents of a tetracycline capsule dissolved in water, gargled, and swallowed), but there are no strong clinical data supporting their efficacy.[9, 10] Topical anesthetics (for example, viscous lidocaine [Xylocaine]) may be helpful when pain is severe; these are only uncommonly necessary.

Oral candidiasis usually presents with white curdlike patches over the tongue and oral mucosa, which may bleed superficially as these patches are scraped from the mucosal surface. This infection may occur de novo, but is more common in diabetics, immunosuppressed or debilitated patients, or patients using antibiotics or corticosteroids (especially topical steroid preparations such as inhalers for asthma or allergic rhinitis) at the time of onset. Unexplained oral candidiasis, especially in a young patient, should raise the question of some type of immune deficiency, especially acquired immunodeficiency syndrome (AIDS). Mycostatin mouthwash (swallowed after rinsing), 100,000 units three times a day, is usually curative. *Chronic atrophic candidiasis* (denture stomatitis) is a more localized process resulting in an erythematous erosion underlying (usually) a poorly fitting denture.

Periodontal infections (or abscesses) present as acute gingivitis with or without localized fluctuance—broad-spectrum antibiotics and dental attention are indicated. *Pericoronitis* refers to acute inflammation of "gum flaps" overlying partly erupted wisdom teeth; dental surgery is often necessary.

Many rare or systemic diseases may also cause oral or pharyngeal ulcerations—systemic lupus erythematosus (SLE), Behçet's disease, syphilis, tuberculosis, neoplasms, pemphigus, pemphigoid, erythema multiforme, Reiter's syndrome, sprue, Crohn's disease, cyclic neutropenia, lichen planus, and many others.[8] Especially when lesions are recurrent or atypical of the common infectious processes discussed above, consultation or biopsy may be indicated.

Occasionally, physical examination of a patient with sore throat will reveal erythema and swelling of the *uvula* alone. Various pharyngeal irritants, especially marijuana, may cause this syndrome; however, it is likely that this represents a localized uvular cellulitis in some patients, since broad-spectrum antibiotics (ampicillin) seem to solve the problem. (This has not been well studied.)

3. *Infectious mononucleosis is not an uncommon cause of sore throat in adolescents,* but the diagnosis is usually suggested by physical examination.* Infectious mononucleosis[11–14] is usually suspected for one of two reasons: (a) When a teenager's sore throat persists for more than 1 week or relapses and recurs over many days (an unusual course in viral or streptococcal pharyngitis), or (b) When posterior cervical, postauricular, axillary, or inguinal adenopathy is palpable (such adenopathy is present in 80 to 90 per cent of mononucleosis patients).

Malaise, persistent fever, generalized lymphadenopathy, splenomegaly, a foul-smelling tonsillar exudate, or palatal petechiae may also be prominent in some cases, but these are less common than are *the classic findings*: the teenager or young adult with fever and persistent sore throat with palpable posterior cervical or postauricular adenopathy. In older adults, the disease is rare and clinical features are often atypical.[15, 16] Table 1–3 illustrates the diagnostic utility of clinical findings and currently available tests for infectious mononucleosis.

The diagnosis of mononucleosis is confirmed by the peripheral blood count or the Monospot test (the latter is less expensive and more convenient than the standard heterophil agglutination test).[17] The peripheral blood count will reveal atypical lymphocytosis in 80 per cent of patients during the first week of illness and in almost 100 per cent by the end of the second week.† The blood count and Monospot test may both be necessary when mononucleosis is suspected, because either test may be nondiagnostic at a particular point in time, but usually one *or* the other will suffice[18] (see Table 1–3). (The Monospot test performed much better than the blood count in one large study.)[19] Other more serious illnesses (toxoplasmosis, rubella, viral hepatitis, syphilis, drug reactions, leukemia, or lymphoma) may rarely produce a similar clinical illness as well as atypical lymphocytosis, but the Monospot test is both sensitive and specific, the more so when performed after 1 to 2 weeks of clinical illness. When the Monospot test (or heterophil agglutination test) remains negative after 2 to 3 weeks of otherwise typical clinical mononucleosis ("heterophil-negative mononucleosis"[21]), cytomegalovirus (CMV) infection is more often responsible than the Epstein-Barr virus (EBV)—the usual cause of mononucleosis. (False-positive heterophil or Monospot tests do rarely occur in patients with lymphoma or malaria or in those taking anticonvulsant medications.) The Monospot test may *remain* positive for a year or

*Mononucleosis is uncommon among adults with sore throat—Aronson and co-workers[25] found only a 2 per cent incidence among 709 patients (mean age 32 years).

†Lymphocytosis may be relative—greater than or equal to 50 per cent of the differential leukocyte count—or absolute—greater than or equal to 4500 mm^3; more than 10 per cent of the lymphocytes will be atypical morphologically.

TABLE 1–3. Infectious Mononucleosis: Diagnostic Utility of Clinical Findings and Tests

	Sensitivity	Specificity	Likelihood Ratio
Clinical Findings			
Fever	.70	.80	3.5 +/.38−
Cervical adenopathy	.90	.60	2.25+/.17−
Splenomegaly	.25	.95	5.0 +/.79−
Palatal petechiae	.25	.95	5.0 +/.79−
Any one of above	1.0	—	— / 0−
Tests*			
White blood cell count/ differential†	.85‡	.98	43+/.15−
Monospot test	.90	.98	45+/.10−
Heterophil test (>1:224)	.90	.99	90+/.10−
Epstein-Barr virus antibody titers (>1:10)	.95	1.0	∞ +/.01−

*Sensitivities will be slightly *lower* during the first week of illness and higher at the *peak* of illness (often 10 to 14 days). Epstein-Barr virus (EBV) antibody titers are .99 sensitive when *mononucleosis* is due to EBV, but this is so in only about 90 per cent of cases.

†At least 50 per cent lymphocytes and ≥10 per cent atypical lymphocytes.

‡Fleisher and associates found a sensitivity of only *.39*.

Source: Based on data from Pantell RH: Ann Intern Med 86:497, 1977; Griner PF: Infectious mononucleosis. *In* Griner PF, et al: Clinical Diagnosis and the Laboratory. Chicago, Year Book Medical Publishers, 1986; Fleisher GR, et al: J Clin Microbiol 17:619–624, 1983; Neiderman JL, et al: JAMA 203:205–209, 1968.

longer following acute infection. More specific serologic testing is available for the various EBV antibodies, but these are useful only occasionally—in the patient with typical clinical mononucleosis whose Monospot or heterophil findings are negative but who "needs to know" or in the patient suspected of relapsing or persistent EBV infection (see p. 22).

Treatment of mononucleosis is usually expectant and symptomatic. (The efficacy of acyclovir treatment is uncertain.) Coexistent streptococcal pharyngitis should be excluded by throat culture or streptococcal antibody testing. The use of ampicillin should be avoided because of the unexplained high incidence of reactions to this drug in patients with acute mononucleosis. Patients should be counseled to avoid contact sports or injuries to the abdomen for the first 2 to 3 weeks of illness, especially when there is palpable splenomegaly, because of the small (but real) risk of splenic rupture.

Corticosteroid therapy, 40 to 60 mg of prednisone a day for 1 week, may produce prompt and dramatic clinical improvement,[22, 23] especially when fever and malaise are debilitating and tonsillar swelling and inflammation make eating and drinking difficult. ("Rebound" of symptoms may occur as steroids are quickly tapered, but this is rare.) Most patients do not require steroid therapy. Definite indications for steroid therapy, however, include pharyngeal obstruction with threatened upper airway closure due to tonsillar hyperplasia (the "kissing tonsil syndrome")[24] and the very rare complications of hemolytic anemia, thrombocytopenia, or neurologic sequelae. Some such patients require hospitalization (upper airway obstruction is the most common reason). Most patients have elevated levels of liver enzymes, but only rarely must this finding be followed or further investigated (e.g., if the patient is frankly jaundiced).

Routine testing for mononucleosis in all patients with sore throat is wasteful.[25] A careful clinical history and examination will usually suggest the diagnosis and allow selective (cost-effective) testing.

Thus, a brief but careful history and examination will usually exclude nonpharyngeal causes of sore throat, infectious mononucleosis, and other obvious oral, dental, head, or neck infections.

CONSIDER AGAIN OUR PATIENT

Phil appears mildly ill. His oral temperature is 38°C. There is no respiratory difficulty. Phil localizes his discomfort to the posterior pharynx and complains of painful swallowing, but he is able to swallow food. The posterior pharynx is erythematous, but there are no pharyngeal exudates, oral mucosal lesions, tonsillar hypertrophy, or membranes. The teeth, gingivae, ears, and thyroid are normal. There are small but bilaterally tender upper anterior cervical lymph nodes. There are no posterior cervical or postauricular lymph nodes, splenomegaly, or axillary-inguinal lymphadenopathy.

What does this mean?

STREPTOCOCCAL OR NONSTREPTOCOCCAL PHARYNGITIS?

I. *Phil appears to have uncomplicated pharyngitis.*

Symptoms are typical of pharyngitis, and there is no specific reason to suspect mononucleosis, referred throat pain (see Table 1–2), or other localized infections. Furthermore, Phil is not very ill—more extreme clinical toxicity, usually manifested by various worrisome symptoms and signs (see pp. 12–20), warrants different considerations. Here the differential diagnosis involves primarily viral and streptococcal pharyngitis.

II. *Although certain clinical features suggest streptococcal pharyngitis, the diagnosis is uncertain.*

Clinicians frequently overestimate the likelihood of streptococcal pharyngitis in patients with sore throat.[26] There are probably several reasons for this.

First, the prevalence of streptococcal pharyngitis in adults is surprisingly low. An "average" prevalence is 10 per cent, but this varies with the clinical setting (see Table 1–6).[26–31]

Second, the sensitivity and specificity of various clinical findings are low, but clinicians often mistakenly inflate the "post-test probability" when tonsillar exudate or cervical adenopathy or fever is present. As Table 1–6 illustrates, the presence of these findings does raise the likelihood of streptococcal pharyngitis (and their absence lowers it), but the sensitivity and specificity of these findings vary in different studies (and different patient populations), and thus so does their predictive accuracy.

Third, clinicians differ in the *importance* they attach to a diagnosis of streptococcal pharyngitis. Some believe that early antibiotic treatment speeds clinical improvement (see below); some attribute more risk to certain types of patients (diabetics, patients with heart murmurs).[32, 33] Clinicians with such "value-induced" biases more often overestimate the probability of streptococcal disease.[26]

Finally, streptococcal pharyngitis (Fig. 1–5) is one of the few causes of sore throat that necessitate any specific treatment. This can be a "psychological bias" for the clinician who wants to intervene actively, i.e., to "cure," not just to reassure.

Since no clinical finding in adults is any more predictive of streptococcal pharyngitis (Tables 1–5 and 1–6) than the flip of a coin (almost 1:1 odds for patients presenting to an emergency room with sore throat who were found to have tonsillar exudate, among whom disease prevalence was very high—26 per cent),[31] attempts have been made to predict streptococcal disease by the presence or absence of *combinations* of clinical findings. Table 1–4 presents this approach in the study by Komaroff and colleagues.[30] Patients were grouped according to the presence of all, any, or none of the three

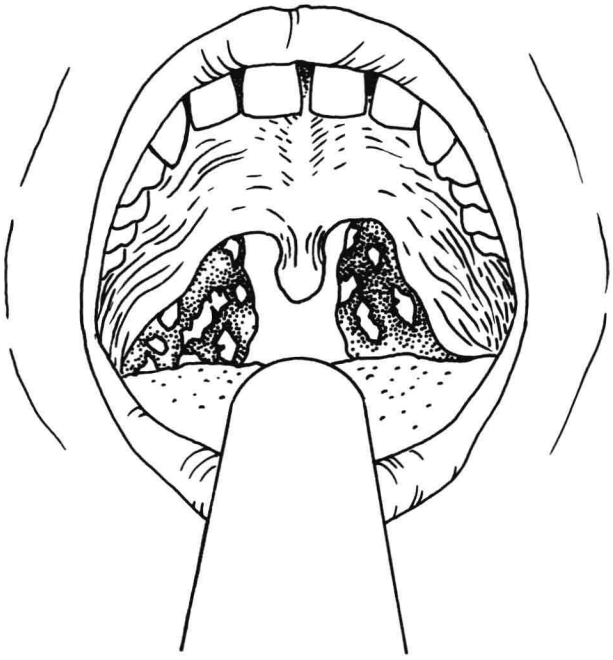


FIGURE 1–5. ***Tonsillar exudate.*** **The tonsils are inflamed and swollen. They are covered with a loosely adherent, yellow exudate. Such an exudate is "typical" of streptococcal pharyngitis but may also be seen in infectious mononucleosis or viral pharyngitis (Table 1–5).**

best "strep predictors"—exudate, adenopathy, and fever. Note that the "high" probability (42 per cent or 2:3 odds) patients who had *all* three findings were few (2 per cent or one in 50), while the "medium" (any finding) and "low" probability (no finding) patients were many (61 per cent, or three in five, and 37 per cent, or two in five, respectively). Just as the presence or absence of any one finding "spreads the odds" toward or away from the probability of strep, identification of patient subsets by a combination of findings does the same, but more reliably. Without the use of the prediction rule, "strep odds" were 1:9 (disease prevalence 10 per cent); subsetting patients according to the rule raises the odds as high as 2:3 for a few patients and as low as 1:30 for many.

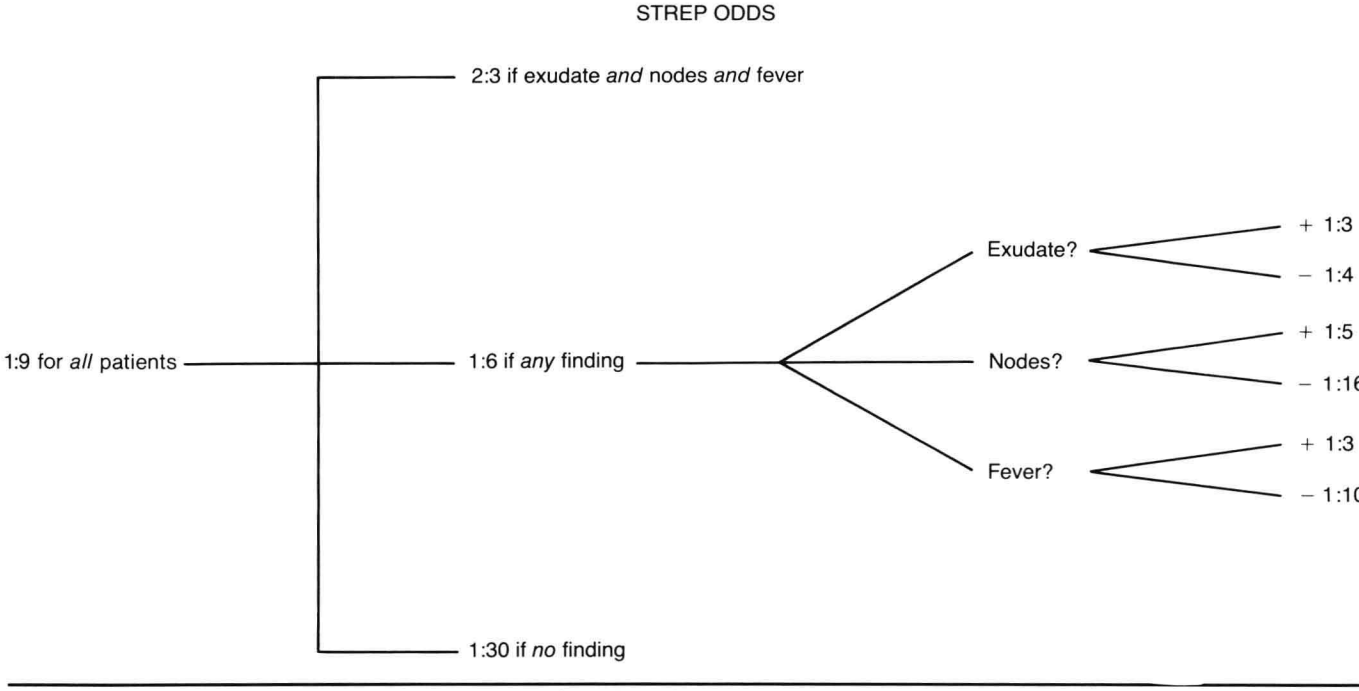
Several such prediction rules have been proposed.[27, 29–31, 34–39] These are clinically useful only if several conditions are met.

First, the clinical findings must be reliable and reproducible. Note how variable were the frequencies of the "strep predictors" in the different studies listed in Table 1–6. Some of this variability is due to differences in clinicians' skill and their interpretation of physical findings.

Second, "transporting" a clinical prediction rule (from one study to a physician's own patient population) may be misleading if differences in disease prevalence are not considered.[40] If Komaroff and co-workers' rule[30] (see Table 1–4) were applied to the population of Wigton and colleagues[31] (disease prevalence 9.7 per cent versus 26 per cent in Table 1–6), it might perform even better. If it were applied to Poses and associates' patients[26] (disease prevalence 4.9 per cent in Table 1–6), it would likely not perform as well.

TABLE 1–4. Findings Associated with Sore Throats in 693 Adults*

Clinical Findings	Number of Patients (Per Cent)	Throat Culture: Group A Streptococcus	ASO Antibody Rise
Exudate *and* nodes *and* fever	14 patients (2%)	42.1%, or 3:4 odds (6 strep:8 no strep)	16.5% (2 patients)
Exudate *or* nodes *or* fever	423 patients (61%)	13.5%, or 1:6 odds (57 strep:366 no strep)	5.6% (24 patients)
No exudate *nor* nodes *nor* fever	256 patients (37%)	3.4%, or 1:27 odds (9 strep:247 no strep)	0.47% (1 patient)



Adapted from Komaroff AL, et al: J Gen Intern Med 1:1–7, 1986.
*Overall Group A *Streptococcus* prevalence 9.7 per cent.

TABLE 1–5. Clinical Findings in 418 Patients with Positive and Negative Throat Cultures

	Throat Culture: + (Group A) Streptococcus (%)	Throat Culture: No Streptococcus (%)
Total	64 (100)	354 (100)
Symptoms		
Rhinorrhea	17 (26)	169 (47)
Cough	11 (17)	169 (47)
Recent exposure to streptococcus	16 (25)	43 (12)
Hearing loss	9 (14)	29 (8)
Signs		
Pharyngeal erythema	63 (98)	299 (84)
Pharyngeal/tonsillar exudate	30 (47)	73 (21)
Swollen tonsils	41 (64)	131 (37)
Enlarged/tender cervical nodes	60 (93)	258 (72)
Temperature: under 37.2°C	33 (52)	238 (68)
37.2°–38.2°C	20 (31)	91 (26)
greater than 38.3°C	11 (17)	22 (6)
Incidence of streptococcal pharyngitis = 64/418 = 15%		

Adapted from Walsh T, et al: Arch Intern Med 135:1493, 1975.

Third, prediction rules are worthwhile only if their application is strategically useful. How does it help to know that "high-risk" patients are more likely to have positive throat cultures? Does this change what we *do*? Note in Table 1–4 that there are ten times as many patients with positive cultures in the "medium-risk" group as in the high-risk group; in fact, there are more positive cultures among the "low-risk" group than among the high-risk group! If the clinical goal is to detect most cases of streptococcal pharyngitis, we would do better to ignore the high-risk group than to ignore the low-risk group! This is counterintuitive but true; the tautologic point is that rules are useful only if we can use them.

Finally, the development of rapid antibody tests for streptococcal disease could render these clinical predictors obsolete.[41] (Some argue that they already render the throat culture itself obsolete.[42]) As many as 10 per cent of throat cultures are falsely negative; some clinicians thus obtain two swabs from each patient. Between 1 and 10 per cent of adults (and probably even more children) are "strep carriers" whose throat cultures will be positive but who do not have streptococcal pharyngitis by any other criteria (clinical findings, antibody titer rises, risk of acute rheumatic fever); such cultures are, in one sense, "false-positive." Probably fewer than half of patients who do have "strep throat" (by both clinical and culture criteria) are at risk for acute rheumatic fever (see Table 1–4), since serial antibody rises develop in only a minority. Thus, the throat culture is a somewhat tarnished "gold standard" whose predictive value is itself far from perfect.

Diagnostic Decisions

What, then, should be done? Should throat cultures be obtained in all patients with sore throat? Should we obtain cultures only from patients whose probability of disease is higher than the strep carrier rate (5 per cent), i.e., not take cultures from the low-risk group? Should we discard throat cultures and use the rapid antibody test? If so, for all patients or only certain risk groups? If cultures are obtained, should antibiotics be prescribed pending the results? If cultures are negative, should antibiotics be stopped, even if the patient has improved? Does it ever make sense to prescribe antibiotics without performing any tests? Can we ever forgo both the

TABLE 1–6. Clinical Predictors of Streptococcal Pharyngitis ("Strep")

Physical Findings	Poses et al.[26] Student Health Center 308 Patients 15 (4.9%) Strep Strep Odds 1:19	Komaroff et al.[30] HMO/Walk-in Clinic 693 Patients 67 (9.7%) Strep Strep Odds 1:9	Walsh et al.[27] Adult Walk-in Clinic 418 Patients 64 (15.3%) Strep Strep Odds: 1:5	Wigton et al.[31] Emergency Room 516 Patients 134 (26%) Strep Strep Odds 1:3
Exudate Present	118 patients (38%)	114 patients (16%)	103 patients (25%)	175 patients (34%)
Sensitivity	.80 (12/15)	.43 (29/67)	.47 (30/64)	.59 (79/134)
Specificity	.64 (187/293)	.86 (541/626)	.79 (281/354)	.75 (286/382)
Odds of strep if exudate present	1:9 (10%)	1:3 (25%)	1:3 (29%)	1:1 (45%)
Odds of strep if exudate absent	1:61 (1.6%)	1:14 (6.6%)	1:8 (11%)	1:5 (16%)
Adenopathy Present	205 patients (67%)	239 patients (34%)	318 patients (76%)	329 patients (64%)
Sensitivity	.93 (14/15)	.61 (41/67)	.94 (60/64)	.80 (107/134)
Specificity	.35 (102/293)	.68 (438/626)	.27 (96/354)	.42 (160/382)
Odds of strep if adenopathy present	1:13 (7%)	1:5 (17%)	1:4 (19%)	1:2 (33%)
Odds of strep if adenopathy absent	1:99 (1%)	1:16 (5.7%)	1:24 (4%)	1:6 (14%)
Fever Present	Not reported in study	42 patients (6%)	33 patients (8%)	229 patients (44%)
Sensitivity		.15 (10/67)	.17 (11/64)	.60 (80/134)
Specificity		.95 (594/626)	.94 (332/354)	.61 (233/382)
Odds of strep if fever present		1:3 (24%)	1:2 (33%)	1:2 (35%)
Odds of strep if fever absent		1:10 (9%)	1:6 (14%)	1:4 (19%)