



An Evidence-Based Approach To Infectious Disease

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Pharyngitis In The ED: Diagnostic Challenges And Management Dilemmas
HIV-Related Illnesses: The Challenge Of Emergency Department Management
Antibiotics In The ED: How To Avoid The Common Mistake Of Treating Not Wisely, But Too Well

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An Evidence-Based Approach To Infectious Disease

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Goals & Objectives: Upon completion of this activity, you should be able to: (1) demonstrate medical decision-making based on the strongest clinical evidence; (2) cost-effectively diagnose and treat the most critical ED presentations; and (3) describe the most common medicolegal pitfalls for each topic covered.

Target Audience: This enduring material is designed for emergency medicine physicians, physician assistants, nurse practitioners, and residents.

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Each action in the clinical pathways section of *Emergency Medicine Practice* receives a score based on the following definitions.

<p>Class I</p> <ul style="list-style-type: none"> • Always acceptable, safe • Definitely useful • Proven in both efficacy and effectiveness <p><i>Level of Evidence:</i></p> <ul style="list-style-type: none"> • One or more large prospective studies are present (with rare exceptions) • High-quality meta-analyses • Study results consistently positive and compelling 	<p>Class II</p> <ul style="list-style-type: none"> • Safe, acceptable • Probably useful <p><i>Level of Evidence:</i></p> <ul style="list-style-type: none"> • Generally higher levels of evidence • Non-randomized or retrospective studies: historic, cohort, or case control studies • Less robust RCTs • Results consistently positive 	<p>Class III</p> <ul style="list-style-type: none"> • May be acceptable • Possibly useful • Considered optional or alternative treatments <p><i>Level of Evidence:</i></p> <ul style="list-style-type: none"> • Generally lower or intermediate levels of evidence • Case series, animal studies, consensus panels • Occasionally positive results 	<p>Indeterminate</p> <ul style="list-style-type: none"> • Continuing area of research • No recommendations until further research <p><i>Level of Evidence:</i></p> <ul style="list-style-type: none"> • Evidence not available • Higher studies in progress • Results inconsistent, contradictory • Results not compelling <p>Significantly modified from: The Emergency Cardiovascular Care Committees of the American Heart Association and represen-</p>	<p>tatives from the resuscitation councils of ILCOR: How to Develop Evidence-Based Guidelines for Emergency Cardiac Care: Quality of Evidence and Classes of Recommendations; also: Anonymous. Guidelines for cardiopulmonary resuscitation and emergency cardiac care. Emergency Cardiac Care Committee and Subcommittees, American Heart Association. Part IX. Ensuring effectiveness of community-wide emergency cardiac care. <i>JAMA</i>. 1992;268(16):2289-2295.</p>
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The Emergency Medicine Practice Clinical Excellence Series Volume VI

An Evidence-Based Approach To Infectious Disease

It is with great pleasure that we bring to you Volume VI of the *Emergency Medicine Practice Clinical Excellence Series: An Evidence-Based Approach To Infectious Disease*. We hope these select articles will engage you in a critical and clinically relevant look at several very interesting topics.

The 4 articles included in this volume update the extensive research and discussion on the diagnosis and management of several infectious disease topics from past issues of *Emergency Medicine Practice*, with all-new recommendations and analysis. In addition to the over 500 original references, 86 new references will bring you up to date on the latest research and guidelines in the field, with distinct, underlined paragraphs indicating the new research and commentary. The list of new references is numbered separately to make further research easier.

The topics for this volume include the diagnostic and therapeutic strategies for ED management of the febrile child, pharyngitis, and HIV-related diseases. The fourth chapter on antibiotics usage in the ED will certainly inform and impact the practice of all emergency clinicians. We believe these selections will stimulate thought-provoking discussion and aid in clinical decision-making.

Since 1999, *Emergency Medicine Practice* has been exceptional in its evidence-based approach to emergency medicine. It seeks to provide the etiology and pathophysiology behind a topic, as well as the full spectrum of literature and evidence on the topic, and to present

it in a readable and clinically relevant way. This differs from the many management guidelines, consensus statements, and analyses that do not illuminate the critical thinking and evidence behind the recommendations.

Over the years, I have appreciated reading *Emergency Medicine Practice* because of its unique mission in reviewing “hot” topics in emergency medicine, written from an emergency physician’s perspective. I hope you enjoy this volume of *The Emergency Medicine Practice Clinical Excellence Series*. I also hope that you will consider and enjoy the future volumes in this series.

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The Young Febrile Child: Evidence-Based Diagnostic And Therapeutic Strategies

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CME Objectives

Upon completing this article, you should be able to:

1. Explain important aspects of the history and physical examination in children with fever.
2. List indications for diagnostic tests in febrile children, including CBC, lumbar puncture, chest x-ray, urinalysis, and urine culture.
3. Describe the risks and indicators of occult bacteremia.
4. Discuss the evidence concerning empiric antibiotic treatment in febrile children.

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Fever is one of the most common reasons young children are brought to the emergency department (ED).¹⁻³ Many parents (and some physicians) are frightened by fever in a child; often they exaggerate its dangers and are overly aggressive in its treatment.⁴⁻⁶ In the early weeks and months of a child's life, this level of concern may be appropriate. Not only is fever less common at that age, but it is also more likely to be associated with a serious bacterial infection, such as meningitis or sepsis.^{7,8} Until the child is about 2 to 3 months of age, findings on physical examination are not sensitive and specific enough to exclude serious bacterial infection with confidence, particularly when the rectal temperature is high ($\geq 39.0^{\circ}\text{C}$ [$\geq 102.1^{\circ}\text{F}$]).^{9,10} In children above age 2 to 3 months, fever becomes both more frequent and less ominous.

This issue of *Emergency Medicine Practice* focuses on the 3- to 36-month-old child who was previously well and who has no serious chronic illness (eg, sickle cell disease, congenital heart disease, severe neuromuscular disease) who presents with fever, defined as a rectal temperature of 38.0°C (100.3°F) or higher (or an axillary temperature of 37.0°C [98.5°F] or higher) as measured at home or in the ED.

A careful history and physical examination will usually identify the child with either an obvious bacterial infection or a characteristic viral infection. But the problem is how to manage the child whose fever has no clearly identifiable source — a scenario fraught with uncertainty, complexity, and controversy. Many different clinical outcomes are possible, and even the most experienced ED clinician cannot predict the results for a particular child. Researchers disagree about even the most fundamental issues regarding the need for diagnostic tests.

When confronted with a febrile child, ED clinicians must ask themselves a series of questions:

1. Should 1 or more diagnostic tests be performed? If so, which ones and in what order?
2. If diagnostic tests fail to confirm a bacterial infection, should empiric ("expectant") antibiotic treatment be prescribed as a precaution?
3. If one decides to treat the child with an antibiotic, should the drug be given orally or parenterally (eg, intramuscular ceftriaxone)?
4. What follow-up care should be arranged?

Although these questions are valid for both the office-based practitioner and the ED clinician, the differences between these 2 settings can result in substantial disparity in diagnostic and therapeutic management.¹¹⁻¹⁵ For one thing, most office-based practitioners must refer their patients to private or hospital-based laboratories for diagnostic tests, whereas such tests are easily performed in the ED setting. For another, office-based practitioners are often familiar with both patient and family, which helps in determining how pertinent specific signs and symptoms are, is useful in adapting the intensity of testing to their personalities and values, and is likely to ensure adequate follow-up.

Despite these differences, however, there are many similarities between the 2 settings. The information gained through diagnostic testing should be identical for both, as is the potential for benefit when the results are accurate and the possibility of harm when they are misleading.

Over the past 2 decades, there has been a distinct shift toward more aggressive management of the young febrile child. As summarized in the practice guidelines developed by experts in the fields of pediatrics, emergency medicine, and infectious disease, this trend includes increased diagnostic testing, more frequent attempts to treat, and more invasive therapies (ie, parenteral rather than oral).^{16,17} Yet is this shift justified? Have outcomes improved as

a result of more aggressive testing and the more liberal use of antibiotics, or does this strategy merely increase costs, ED length of stay, and discomfort for both the young patients and their parents?

In this issue we will review the evidence concerning the epidemiology and etiology of fever in young children, discuss the diagnostic value of specific information gleaned from the history and physical examination, and present the advantages and disadvantages of individual diagnostic tests. We will also examine the risks and benefits of the empiric use of oral and parenteral antibiotics and the importance of follow-up. Finally, based on this evidence, we propose a management algorithm for this common but complex clinical problem.

Epidemiology And Etiology

When a child has a fever, parents often seek a doctor's advice. Two-thirds of all children see a physician for a febrile illness during the first 2 years of life.¹⁸ From the ED perspective, as many as one-third of pediatric visits involve fever, and the majority of these visits are by children between 3 and 36 months of age.^{1,2}

Possible Causes Of Fever

Fever in the young child is likely to be due to one of the following types of infectious illness:

1. Clinically identifiable viral infections
2. Clinically evident bacterial infections
3. Other infectious illnesses (presumably viral)
4. Occult bacterial infections

In a small number of children, however, fever may be caused by malignancy, parasitic infections, collagen vascular, or other inflammatory diseases (eg, Kawasaki disease), drug effects, or other unusual causes.

Clinically identifiable viral infections include varicella, measles, herpes simplex, gingivostomatitis, croup, herpangina, and hand-foot-and-mouth disease. With the exception of viral croup, most of these infections involve characteristic rashes. Other exanthems, which are often maculopapular, may be secondary to a viral infection, may represent an allergic reaction, may be a heat rash, or may be caused by local irritation. Roseola becomes clearly identifiable only in retrospect (ie, after the fever resolves), since the rash is not evident at the time of presentation.

Clinically evident bacterial infections can be readily diagnosed from the history and physical examination alone. They include most cases of otitis media and many cases of pneumonia, meningitis, septic arthritis/osteomyelitis, lymphadenitis, and dysentery-like bacterial enteritis.

The third category comprises nonspecific viral infections, although in most cases no virus is identified. These infections are manifested as an upper

respiratory infection (URI), bronchiolitis/asthma, viral gastroenteritis, mixed respiratory and gastrointestinal infections, fever accompanied by rash, and fever only. Malaria, other parasitic diseases, and rare fungal infections can sometimes resemble these nonspecific viral infections.

The fourth category, occult bacterial infections, includes bacteremia; the vast majority of children with urinary tract infection (UTI); and clinically silent cases of pneumonia, meningitis, septic arthritis/osteomyelitis, bacterial enteritis, and sinusitis. Pelvic or abdominal abscesses are considerably more rare. It is this group of infections that poses the greatest challenge to diagnostic and therapeutic management. Because the infections are occult, they cannot be diagnosed with confidence based on the history and physical examination alone. In the child with a fever that has no obvious source, the physician should consider the possibility of a UTI — a common and important clinical problem in infants and young children, with a prevalence of 5.3% among febrile infants seen in the ED. As many as 17% of white female infants with a rectal temperature of 39.0°C (102.1°F) or higher may have an infection of the urinary tract.¹⁹

Occult Bacteremia

In some children for whom the history and physical examination offer no clue to the cause of their fever, diagnostic testing, such as urinalysis or chest radiography, may be more revealing. For others, these tests are unproductive, since the source of the fever is a blood infection — occult bacteremia.

In perhaps 1% to 3% of children with a temperature of 39.0°C (102.1°F) or higher for which there is no obvious cause and no evidence of toxicity, bacteria will be found on blood culture. In a recent study of over 9000 children (including children with otitis media), the incidence of occult bacteremia was 1.6%, with no cases of *Haemophilus influenzae* type b (Hib).²⁰ Although bacteremia due to Hib has decreased since the widespread use of the Hib conjugate vaccine, this decrease does not explain the lower prevalence of occult bacteremia in more recent studies. Of the 2% to 3% of children with occult bacteremia, approximately 3% will go on to develop a serious bacterial infection such as pneumonia, osteomyelitis, or meningitis. Thus, 1 child in 1000 ($0.03 \times 0.03 = 0.0009$) who looks clinically well with a temperature of 38.9°C (102.0°F) and no focus of infection will progress to a serious illness over the next several days.

How do we prevent occult bacteremia or detect it at an early stage? How much should we spend on this effort? And how many well children should be tested by means of blood cultures and receive parenteral antibiotics to deal with this dilemma? The answers to these questions will be found in the review that follows.

Evaluation In The ED

History

When a child presents to the ER with fever, his or her age becomes a valuable piece of diagnostic information. This is true even within the restricted age group of 3 to 36 months. In particular, children under 12 months of age are at considerably higher risk than are older children for UTI and meningitis,²¹⁻²³ whereas those over 24 months of age are at higher risk for sinusitis.²⁴ Occult bacteremia is less common in children under 6 months of age (because of the presence of protective maternal antibodies) and in those over 24 months of age (because of acquired immunity).²⁵

Race and gender are also of value in the differential diagnosis of UTI, since whites²² and females^{22,26,27} are at higher risk. Among males, especially those less than 6 months of age, the risk of UTI is much higher among those who have not been circumcised.^{22,28-31}

Although infrequently studied, the duration of a fever can be of some diagnostic value. Parents should be questioned about the course of the child's fever — ie, has it occurred daily or have there been 1 or more afebrile days? In the latter case, a second febrile illness (usually viral) is probably the cause. On the basis of clinical experience and limited studies, the child who remains febrile for 5 days or more (as documented by daily thermometry) and who is not taking antibiotics probably does not have an occult meningitis or occult bacteremia.³²

Prolonged fever generally indicates a viral illness or an occult bacterial process such as pneumonia, UTI, bartonellosis, tuberculosis, or sinusitis.³³⁻³⁵ In the largest prospective study of occult bacteremia to date, involving 6680 children 3 to 36 months of age, those with temperatures of 39.0°C (102.1°F) or higher were significantly more likely to have bacteremia if their fever lasted less than 1 day than if it lasted for 1 day or more (3.8% vs 2.4%, respectively).³²

In some cases parents will report a child's fever based on tactile evidence alone, without the aid of thermometry. Clinicians should not regard this information as trivial. In a study conducted at 2 inner-city hospitals, the nonthermometric detection of fever had a sensitivity of 84% and specificity of 76%.ⁱ

Obviously, symptoms accompanying the current illness are of diagnostic value. Runny nose, sneezing, and cough occur frequently in the child with an upper respiratory tract infection (URI); however, cough in isolation, especially when accompanied by a high fever and recurrent vomiting, makes an occult pneumonia more likely.^{36,37} Although the vast majority of children with cough and fever have a viral illness, when these findings are combined with vomiting and diarrhea, viral gastroenteritis should be suspected. Bloody or purulent diarrhea suggests

bacterial enteritis. Irritability, excessive sleepiness, and other changes in mental status, though nonspecific signs, may indicate occult bacterial meningitis,⁹ although 1 study found no such increase.³⁸ Finally, the true significance of a child's pulling at his or her ears is not known. According to some pediatric experts, such behavior does not suggest otitis media any more than playing with the toes signifies osteomyelitis of the feet.¹⁵¹

Contrary to conventional wisdom, reduced appetite and/or activity is not helpful in considering the differential diagnosis of fever. The same inflammatory cytokines that are responsible for the release of prostaglandin E in the hypothalamus and the subsequent development of fever (ie, interleukin-1b, interleukin-6, and tumor necrosis factor) also lead to hypothalamus-mediated anorexia and weakness.^{39,40}

Sometimes the absence of certain symptoms may be helpful. Some authorities have found that the lack of respiratory or gastrointestinal symptoms in febrile infants increases the probability of UTI. However, clinicians must remember that signs and symptoms are poor discriminators of UTI.

The ED clinician should ask the parents directly but in a sympathetic and nonjudgmental manner whether their child has already been seen by another physician for this illness, since they may be reluctant to volunteer such information for fear of appearing to be "doctor-shopping." Inviting the parent to relate another physician's diagnostic impressions and treatments will often provide useful information.

If the child has seen a different ED clinician or other physician, it is important to determine whether he or she was given antibiotics during those visits. Ask specifically whether the child has been taking antibiotics, since he or she may already be taking a prescribed antibiotic or one left over from a previous illness or prescribed for someone else in the family. In 1 study, nearly 20% of 2-year-olds or younger children who were seen in the ED for a presumed infection were found to have antibiotics in their urine even though 80% of their parents denied having administered these drugs to them.⁴¹ In another study, urine assays were positive for antibacterial activity in 16.5% of the children who presented to a pediatric ED, and again only half the parents admitted that they had given their children antibiotic medications.⁴²

Knowing whether or not a febrile child is already taking antibiotics is useful because these medications may affect the results of blood or urine cultures. Such information may also have important implications when one is considering the need for lumbar puncture as well as the interpretation of spinal fluid analysis.

A history of day-care attendance and close contact with other potentially infected persons can be valuable. Exposure to known cases of URI, gastroenteritis, or febrile illnesses accompanied by a rash increases the likelihood that the child with compatible

symptoms is similarly infected. A history of travel can be helpful in diagnosing or ruling out malaria, other parasitic diseases, and bacterial enteritis.

As for past history, the ED clinician must determine whether the child has had any significant medical problems. Previous UTI increases the likelihood that this same infection is causing the fever in the current illness,²² especially if the child has documented vesicoureteral reflux, abnormal urodynamics, or urinary tract obstruction. Similarly, a history of lobar pneumonia or right middle-lobe collapse in a child known to be asthmatic should alert the clinician to the possibility of a recurrence, even in the absence of suggestive signs and symptoms.

To complete the history, ask the parents about the child's birth, especially regarding prematurity and intubation, since these may be associated with later pulmonary or tracheal infections. Determine whether the child is at risk for immunodeficiency because of sickle cell disease, HIV infection, or other acquired or congenital syndromes. The unvaccinated child is at higher risk for a wide variety of infectious diseases, such as varicella, measles, and *H influenzae* infection.

Increasing numbers of parents rely on the vaccination of other children to confer protection on their own children (a concept known as "herd immunity"), but this phenomenon has also contributed to the loss of herd immunity. For example, the prevalence of whooping cough is increasing because parents are refusing to allow their children to be vaccinated against pertussis.ⁱⁱ

Physical Examination

A careful physical examination is essential when a child appears "toxic," exhibits altered mental status or meningeal signs, or has a clinically recognizable bacterial or viral infection. Certain specific features merit particular attention.

Body Temperature

The child's temperature at presentation is of diagnostic value even if an antipyretic has been given shortly before the visit. High fevers (> 39.0°C [$> 102.1^{\circ}\text{F}$]) are associated with a greater risk of occult bacterial infection, although the vast majority still have a viral etiology.^{22,26,43} Very high fevers may be significant. In 1 small study, more than half of all children with a rectal temperature greater than 41.1°C (106.0°F) had serious disease, and results of peripheral-blood studies did not correlate reliably with the final diagnosis or need for admission.⁴⁴

Temperature correlates loosely with the presence of occult pneumococcal bacteremia. Occult bacteremia is found in only 1.0% to 1.8% of those with temperatures of 39.0°C to 39.9°C (102.1°F to 103.7°F), in 2.0% to 3.2% with temperatures of 40.0°C to 40.9°C (103.9°F to 105.6°F), and in 2.8% to 4.4% with temperatures of 41.0°C (105.7°F) or greater.²⁰ It is not clear why these rates of occult bacteremia are

much lower than those reported in earlier studies, and they are expected to drop precipitously once immunization with conjugate pneumococcal vaccine becomes routine.

It was once thought that a reduction in temperature in response to acetaminophen or other antipyretics had diagnostic implications. This myth may be responsible for the outdated practice of keeping a child in the ED to see whether the temperature comes down. A response to antipyretic therapy does not indicate that an occult bacterial infection is less likely.⁴⁵⁻⁴⁹ In fact, children with serious bacterial illnesses may defervesce with antipyretics, whereas children with minor viral illnesses may remain febrile despite adequate doses.

The rectal temperature is the most reliable method in the ED setting. Although some ED clinicians use tympanic thermometry to check for fever in children, numerous studies question the reliability of such devices.⁵⁰⁻⁵³ Nevertheless, if a tympanic, forehead, oral, or axillary measurement indicates an elevated temperature, the child has a fever, although the converse is not necessarily true.

Vital Signs

Changes in heart rate and blood pressure, shaking, chills, and flushing or pallor are probably related more to the magnitude of the fever and its direction (increasing or decreasing) than to its cause. Nonetheless, clinicians should certainly initiate aggressive treatment when vital signs are abnormal and the child's general appearance is poor.

General Appearance

One of the most important guides in assessing febrile infants and children is their general appearance. According to the Yale Observation Scale, developed in 1982, children who appeared well (scores of 6 to 10) had a less than 3% probability of harboring serious illness; among those who were moderately ill (scores of 11 to 15), the rate of illness was 23%; and those with scores above 15 had a 93% probability of having a serious illness.⁵⁴ (See Table 1.) For well-appearing febrile infants and children with temperatures of 39.0°C (102.1°F) or higher, the lowest possible Yale Observation Score (an assessment score for febrile infants used to predict serious bacterial illness) carries a 2.5% probability of bacteremia; at scores of 8 or 9 and 10 or higher, the respective risks of occult bacteremia are 4.7% and 5.7%.⁵⁵

Children with meningitis have a significantly higher Yale Observation Score (mean score 18) compared with febrile children without meningitis (mean 8). Although the administration of acetaminophen will generally improve the appearance of a febrile child who does not have a serious illness, defervescence will not lead to improvement in the child with meningitis.⁴⁷

In evaluating the general responsiveness of a child with fever, some ED clinicians believe that a set of car keys can be more valuable than even the stethoscope or otoscope. The well-appearing infant will visually track the keys, the toddler will grab for them, and the older child will play catch with them. (If the car is a Saab or Lexus, the febrile teen may try to take them.) The examiner's inability to elicit play or a smile from the febrile child should prompt serial physical examinations, diagnostic testing, or both.

Head, Eyes, Ears, Nose, And Throat

In addition to the presence or absence of a smile, the child's head, eyes, ears, nose, and throat (HEENT) should be examined for important clues as to the child's condition. In younger children, a bulging fontanelle in a toxic-appearing child means meningitis until proven otherwise. Mental status and neck suppleness should be carefully evaluated in children of all ages as clues to possible meningitis. Importantly, the presence of nuchal rigidity (stiffness

of the neck) has a diagnostic sensitivity for bacterial meningitis of 27% for infants 0 to 6 months of age, which rises to 71% at ages 7 to 12 months, 87% at ages 13 to 18 months, and over 95% for infants older than 18 months.⁵⁶

Conjunctival infection is usually seen with viral illnesses and possibly Kawasaki disease. Redness of the conjunctivae, lips, tongue, palms, and soles is a useful sign in diagnosing Kawasaki disease, especially in the presence of enlarged cervical nodes and prolonged fever (5 days). (See Table 2.) The combination of conjunctivitis and an inflamed throat suggests the diagnosis of pharyngeal-conjunctival fever, a common viral illness. Copious rhinorrhea often accompanies a URI, whereas unilateral purulent nasal discharge should prompt a search for a foreign body. Careful inspection of the tympanic membranes is essential for diagnosing otitis media, which is usually (but not always) found prior to or in tandem with a respiratory infection. Since any crying child can have a red ear, pneumatic otoscopy is more accurate for detecting otitis media than is inspection alone.⁵⁷

Examination of the throat and mouth can be especially revealing. Ulcerations on the lips, tongue, or oral mucosa essentially confirms the presence of a viral infection, usually herpetic, and parents will usually mention that the child has been drooling or not eating. Exudative tonsillitis in a young febrile child is almost always of viral origin. The incidence of group A streptococcal infection in 1 study of children under 2 years of age with pharyngitis was no greater than that in asymptomatic controls.⁵⁸

Additional Observations

Examination of the chest should include measuring the child's respiratory rate and assessing the level of respiratory distress. Signs suggestive of pneumonia include rales, rhonchi, wheezing, retractions, grunting, nasal flaring, and focally decreased breath sounds.⁵⁹ Tachypnea has the highest positive and negative predictive values for abnormalities on chest x-ray.⁶⁰ In children without asthma, a respiratory rate of 50 or more breaths per minute and indrawing of the chest are excellent predictors of pneumonia, in which auscultation and percussion are 90% sensitive.⁶⁰

Close examination of the skin is useful in diagnosing meningococemia and typical (but nonspecific)

Table 1. Yale Observation Scale

Observation item	Normal (1 point each item)	Moderate impairment (3 points each item)	Severe impairment (5 points each item)
Quality of cry	Strong or none	Whimper or sob	Weak or moaning, high-pitched, or hardly responds
Parental stimulation	Cries briefly or no cry and content	Cries off and on	Persistent cry with little response
State variation	Stays awake or awakens quickly	Eyes close briefly, then wakes or awakens with prolonged stimulation	No arousal and falls asleep
Color	Pink	Pale extremities or acrocyanosis	Pale, cyanotic, mottled or ashen
Hydration	Skin/eyes normal and moist membranes	Mouth dry	Skin doughy or tented and/or sunken eyes
Response to social overtures	Smiles or alerts	Brief smiles or alerts	No smile, anxious, dull, no alerting

The total of these items corresponds as follows:

Appears well (score, 6-10)

Moderately ill (score, 11-15)

Toxic appearing (score, >15)

Table 2. Criteria For Kawasaki Disease

- Fever for at least 5 days
- Bilateral conjunctival injection (painless, no exudate)
- Mucous membrane changes (pharyngitis, red fissured or cracked lips)
- Edema or erythema of palms or soles
- Rash (polymorphous and truncal)
- Cervical adenopathy with at least node > 1.5 cm

maculopapular viral eruptions. Look for the classic lesion of varicella (“a dew drop on a rose petal”), which in its early stage might be limited to only a few unassuming vesicles. Petechiae are especially noteworthy, since a toxic-appearing child with fever and petechiae must be considered a medical emergency and requires antibiotics without delay. However, the vast majority of febrile children with petechiae do not have serious disease. In 1 study, less than 2% of such children had bacteremia or clinical sepsis; all children with bacteremia appeared ill.⁶¹ Petechiae confined to the face, neck, and chest above the nipple line are not infrequent in children with cough. In 1 report, no febrile child with petechiae limited to above the nipple line had invasive disease.⁶² Of course, meningitis or sepsis should be considered in any ill-appearing child regardless of the pattern of the rash. Macular purpura occurring anywhere on the body of a child with fever should be presumed to be meningococcal until proven otherwise.

Finally, for children who are willing and able to walk, the gait should be examined; the presence of a limp increases the likelihood of bone or joint infection in the lower extremities.

Diagnostic Studies

Yield And Predictive Values

The history and physical examination are cost-effective and essentially painless and offer a high yield. The same cannot always be said of diagnostic tests. When contemplating whether or not to obtain 1 or more laboratory tests, the ED clinician must consider not only their differential diagnostic value (the “pros”), but also their expense and potential for harm (the “cons”).

To the ED clinician, the positive and negative predictive values of a test are of more practical concern than are the mathematical standards of sensitivity and specificity, since the predictive values depend on the pretest probability of a disease — an estimate of which is best made based on the prevalence of the disease in conjunction with the results of the history and physical examination. With a low pretest probability of a disease, a particular diagnostic test may yield false-positive results, thus suggesting a disease the child does not have. With a high pretest probability, a false-negative test may steer the clinician away from the correct diagnosis.

Effect On Management

Before a test is ordered, the ED clinician should have a strategy for testing and should decide whether the test result is likely to change what he or she plans to do for the child. In 1 interesting study, 75% of pediatric ED clinicians ordered a complete blood count (CBC) in the evaluation of a child with a fever ($> 39.0^{\circ}\text{C}$ [$> 102.1^{\circ}\text{F}$]) the source of which was not known, yet the majority did not use the results to guide their management plan in any way.⁶³ If the

result of a test will not influence management, consider skipping the test.

Deciding What Tests To Order

The type and number of tests ordered to evaluate a febrile child may be a matter more of style than of science.⁶⁴ Some physicians may by nature be risk-minimizers (conversely, some say test-maximizers), whereas others are test-minimizers (hopefully not risk-maximizers!). The literature cannot be definitive about which approach is ultimately better for the child—only about which is more expensive. The most recent literature does suggest that there is some variation among ED clinicians with regard to laboratory testing for the febrile infant.ⁱⁱⁱ This study, conducted at a tertiary care center, suggested that in infants 2 to 4 months old, blood and urine tests were ordered routinely, but the rates at which cerebrospinal fluid testing was ordered differed widely.

Test ordering correlates with many factors that have nothing to do with the patient. Physicians with 10 or more years of experience order fewer tests on febrile children, unless they are accompanied by a physician-in-training (particularly during July).⁶⁵ Even the location of the examining room has an impact. The same physician seeing a febrile child in the Fast Track tends to order fewer tests when compared to seeing them in a room located elsewhere in the same ED. These findings are not explained by differences in patient ages, vital signs, or demographics.⁶⁶

The most common tests ordered in the ED may include the CBC and differential blood count, the erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP), in addition to urinalysis and chest radiography. ED clinicians may also order cultures of the throat, urine, blood, or stool. The authors argue that the single most-important test in the febrile child remains the lumbar puncture.

Markers Of Inflammation: CBC, ESR, And CRP Indications

The indications for measuring these inflammatory markers remain unclear. Some clinicians use the results of these tests to determine when to order a blood culture, some use them to guide empiric antibiotic therapy, and some do both. However, the usefulness of these tests in the management of the febrile child is hotly debated.

Pros

It has been shown repeatedly that a high white blood cell count ($\text{WBC} \geq 15,000/\text{mm}^3$) occurs 2 or 3 times more frequently in children with bacterial infections than in those with viral infections.^{27,43,67-69} An elevated ESR or CRP⁷⁰⁻⁷³ contributes diagnostic information independent of the total white cell count; the evidence is less clear that an elevated

“band” (unsegmented neutrophil) count contributes independently to the diagnosis.^{27,68}

For a patient who looks well but whose fever lasts longer than 12 hours, laboratory testing may assist in the decision for further work-up and/or admission. It has been suggested by 1 group of researchers that the finding of inflammatory markers in conjunction with a fever of more than 12 hours’ duration correlates positively with a diagnosis of serious bacterial infection.^{iv} This prospective study involved 128 children 1 to 36 months of age with fever of unknown source and suggested that this correlation was stronger for CRP than for the WBC count or the absolute neutrophil count. The 12-hour cutoff for CRP may be based on the kinetics of this biologic marker.

Cons

Despite the more frequent occurrence of high WBC counts in children with occult bacterial infections, the specificity (~75%) and sensitivity (~60%) of this blood test are too low — ie, the test is associated with many false-positive and false-negative results, respectively. In addition, the test is painful, even if obtained by fingerprick rather than venipuncture. The CBC (and especially the ESR and CRP) entail considerable waiting time by the child and family before the clinician is informed of the results.^{74,75} Although children with an elevated WBC count ($\geq 15,000/\text{mm}^3$) have a slightly greater chance of having bacteremia than those with a count in the normal range, this test is not sensitive and not very specific. WBC counts at or above the $15,000/\text{mm}^3$ threshold fail to identify 14% to 21% of children with bacteremia.^{20,25}

The CBC has been suggested as being useless at distinguishing between occult bacteremia due to *Neisseria meningitidis* and viral illnesses.⁷⁶ Perhaps most importantly, the majority of children with bacterial meningitis have leukocyte counts below this threshold ($< 15,000/\text{mm}^3$).^{77,78} Black children with meningitis are even less likely to have an elevated peripheral leukocyte count than are white children.⁷⁹ Although the CBC alone should never be used to determine the need for lumbar puncture, a high WBC count will sometimes tip the balance in favor of this procedure when the findings on history or physical examination are not reassuring. However, as stated above, ED clinicians should take into account the duration of the illness.

Ordering a CBC may increase costs without providing a benefit to the child. One survey asked 294 pediatric, family, general, and ED physicians how they would manage a febrile infant with no focal source of infection. The respondents were randomly assigned to review a case scenario with either a normal or an elevated WBC count. Knowledge of an elevated WBC count increased the likelihood of their ordering additional tests (and doubled the attendant costs) but did not otherwise influence their man-

agement plan in most cases (although some clinicians chose a more aggressive strategy based on an elevated WBC count alone).⁸⁰

Like any other diagnostic test, inflammatory markers should be measured only if some management decision (eg, further testing, hospital admission, administration of an antibiotic or other treatment) will be affected by the result.

Urinalysis

Indications

Although some authors have argued that urine odor, frequency, dysuria, and other symptoms are useful in the diagnosis of UTI,²¹ empiric data are limited or nonexistent. Few practitioners consider these findings to be of value in the age group under discussion. Because a physical examination to detect UTI in febrile infants and young children is insensitive, urinalysis is recommended for girls and for uncircumcised boys under 2 years of age who have fever of unknown source. (See Table 3, page 12.) Several methods are used to collect urine, and their respective advantages and disadvantages are discussed below.

Pros

Pyuria detected by dipstick leukocyte esterase testing or on microscopic examination has a sensitivity of approximately 80% to 85% and a similar specificity.^{81,82} The nitrite test provides better specificity but a much lower sensitivity.^{81,82} The dipstick test in particular is easy to perform. A Gram stain of an unspun urine sample is over 95% accurate for detecting UTI, although the degree of accuracy depends on the operator and the site. With regard to simple urinalysis, the available evidence is not sufficient to allow conclusive statements about the sensitivity and specificity of clean-voided bag specimens versus specimens obtained by catheter or suprapubic aspiration. How the specimen is obtained, however, has important implications for culture testing. Bag urine specimens are probably adequate for detecting pyuria or for nitrite testing.

Cons

The waiting time can be considerable for a bag urine specimen, since several hours may elapse before the child spontaneously voids.^{74,75} The microscopic examination often entails additional waiting time if the urine sample is sent to a hospital laboratory, and this method does not substantially improve the sensitivity or specificity over the dipstick alone.^{82,83} In addition, if the results of a bag specimen urinalysis are abnormal, a follow-up urine culture of a second specimen obtained by catheterization or suprapubic aspiration will be needed to reduce the risk of contamination.⁸⁴ The American Academy of Pediatrics echoes this finding by stating that in a child under the age of 2 for whom antimicrobial therapy is to be initiated, UTI should not be diagnosed by a bag

specimen.^v Moderate degrees of pyuria can occur in febrile children even in the absence of a UTI.⁸⁵

Urine Culture

Indications

A urine culture should always be obtained when the urinalysis is positive for significant pyuria, nitrites, leukocyte esterase, or bacteria. A culture is also in order for children who are admitted for antibiotic therapy for suspected bacteremia or generalized sepsis.^{86,87}

Pros

A positive urine culture based on a specimen obtained via catheter or suprapubic aspiration is diagnostic of UTI, although both these collection methods pose a low risk of contamination. Prompt diagnosis by this test allows earlier treatment and will reduce the risk of renal scarring if treatment is initiated within 4 days of UTI onset.⁸⁸ Proper ED evaluation can also lead to early detection and surgical treatment of renal anomalies and may reduce the long-term risks of hypertension and end-stage renal disease.^{89,90} The most common benefit of early diagnosis is more rapid relief of symptoms.

Table 3. Summary Of The American Academy Of Pediatrics Practice Parameter Regarding The Diagnosis Of The Initial Urinary Tract Infection In Febrile Infants And Young Children

1. Consider UTI in young children 2 months to 2 years of age with unexplained fever.
2. In young children 2 months to 2 years of age with unexplained fever, assess the degree of toxicity, dehydration, and ability to retain oral intake.
3. If the child is ill enough to require immediate antibiotics, obtain a urine specimen by SPA or transurethral bladder catheterization—not by urine collected in a bag.
4. If the young child with unexplained fever does not require immediate antibiotics, there are 2 options:
 - Option 1: Obtain and culture a urine specimen collected by SPA or transurethral bladder catheterization
 - Option 2: Perform a urinalysis on a urine specimen obtained by the most convenient means (including a bagged specimen). If this suggests a UTI, collect a urine specimen for culture using SPA or catheterization; if urinalysis does not suggest a UTI, the physician does not need to give antibiotics. However, a negative urinalysis does not rule out a UTI.
5. The diagnosis of a UTI requires a urine culture.

Adapted from: Anonymous. Practice parameter: the diagnosis, treatment, and evaluation of the initial urinary tract infection in febrile infants and young children. American Academy of Pediatrics. Committee on Quality Improvement. Subcommittee on Urinary Tract Infection. Pediatrics. 1999;103(4 Pt 1):843-852.

Cons

Culture of a bag urine specimen is highly likely to be contaminated, which can lead to unnecessary follow-up, treatment, radiologic investigation, and even hospital admission.⁸⁴ Obtaining a specimen by catheter or suprapubic aspiration, however, causes discomfort or even pain.⁷⁵ Moreover, the results are not obtained for at least 24 to 48 hours, and microbial sensitivity results often take another day or longer. There is a slight risk of introducing infection through a catheter or needle,^{91,92} and these more intrusive procedures are both associated with the (rare) risk of trauma to the urethra and/or bladder.^{93,94}

Chest Radiography

Indications

Because cough and fever alone do not mandate obtaining a chest x-ray, the results on physical examination should direct the search for pediatric pneumonia.

In 1997, a panel of experts in pediatrics, infectious disease, and microbiology concluded that the absence of certain findings — ie, respiratory distress, rales, diminished breath sounds, and tachypnea (> 60 breaths/min for neonate, > 50 breaths/min for infants age 1 to 12 months, and > 40 breaths/min for children age 1 to 5 years [using World Health Organization criteria]) — accurately excluded pneumonia.⁹⁵ According to a more recent prospective validation trial, however, clinicians who used these criteria detected only 45% of pneumonia cases in children under 5 years of age.⁹⁶ This being said, the vast majority of all cases of childhood pneumonia are viral rather than bacterial.

Indications for chest radiography in febrile children over 3 months of age include

- Respirations \geq 50 breaths per minute for ages 3 to 12 months
- Respirations \geq 40 breaths per minute for ages 1 to 5 years
- Nasal flaring
- Chest retractions
- Grunting
- Diminished breath sounds
- Rales

Note that wheezing is not considered an indication for a chest x-ray in the detection of pneumonia, and this recommendation is supported by recent data.^{vi}

One study from 1999 suggested that chest radiography should be routinely carried out in young children with a temperature of 39.0°C (102.1°F) or higher along with unexplained leukocytosis (WBC count \geq 20,000/mm³) despite the absence of respiratory findings.⁹⁷ This suggestion contradicts the results of multiple other studies,^{59,60} and the study also had several important sources of bias — eg, the indications for obtaining (or not obtaining) a CBC

were not studied, residents rather than attending physicians performed the majority of clinical assessments (56%), and radiologists were not blinded to the clinical information.

Pros

A chest radiograph is very sensitive for pneumonia and is usually well tolerated by children and their parents.⁷⁵ It offers a prompt diagnosis and earlier treatment, hence earlier relief of symptoms.

Cons

Chest radiographs are associated with many false positive results, and interobserver agreement about findings is poor, even among experts in radiology.⁹⁸⁻¹⁰⁰ Moreover, in the age group under consideration, most infiltrates — even large and asymmetric ones — are more likely to have a viral rather than bacterial etiology.^{98,101} Finally, the test is moderately expensive.

Blood Culture

Indications

The indications for blood culture in febrile children remain unclear. In children with a known source of infection, such as pneumonia, pyelonephritis, or cellulitis, the results of blood cultures rarely change management.

In a study that included nearly 1000 children with pneumonia, blood samples were cultured in 44% of cases and results were positive in less than 3%. All these children were started on appropriate antibiotics before culture results were available.¹⁰² In the case of pyelonephritis, urine culture rather than blood culture provides the best source of information regarding the pathogen. In a study of children and adults with pyelonephritis, blood cultures had no impact on clinical management; in only 1 instance (0.2%) did the blood culture contain a pathogenic organism not found in the urine (which happened to be susceptible to the antibiotic selected).¹⁰³ In this post-*H influenzae* era, blood cultures are not cost-effective for the child admitted to the hospital with cellulitis.¹⁰⁴ In the article by Rudinsky et al,^{vii} blood culture results were positive less than 1% of the time in febrile patients with a temperature greater than 39.1°C (102.3°F).

Despite these statistics, which show little or no impact on management, blood cultures are frequently performed in children hospitalized for an infectious disease. The usefulness of blood cultures in a child with presumed occult bacteremia is even less clear, as described below.

Pros

A blood culture found to be positive for a known pathogen is highly specific and reasonably sensitive for bacteremia, although bacteremia may be intermittent (thus leading to occasional false-negative

culture results).⁹⁸ The major advantage of the blood culture is that diagnosis of bacteremia before the onset of meningitis or other serious complications can theoretically prevent such complications. (See the **Empiric Antibiotic Therapy** section, page 14.) Increasing the volume of blood inoculated into culture bottles (9.5 mL rather than 2.0 mL) improves the detection of bacteremia in pediatric patients and spares the family the cost and pain of an additional venipuncture.¹⁰⁵

Cons

The blood culture usually requires 24-36 hours to obtain a result, and most cases of bacterial meningitis have already developed by that time. Pneumococcal bacteremia is often transient. If the temperature persists at the time that the blood culture returns positive, such knowledge usually results in a repeat physician visit and (often) an unnecessary hospitalization and parenteral antibiotic treatment.^{106,107} The hospitalization and treatment are usually unnecessary, because pneumococcal bacteremia generally clears spontaneously by the time the child is reevaluated or would do so subsequently even in absence of treatment.¹⁰⁶⁻¹¹¹

Blood cultures entail considerable expense, and the negative impact of false-positive cultures is significant. Over 20% of pediatric blood cultures deemed positive may be falsely positive. This leads to increased costs, unnecessary hospitalizations, excessive antibiotic therapy, and additional testing.¹¹² Contaminants that cause false-positive results add \$642 per true pathogen recovered on culture—a factor that should be considered in cost/benefit analyses regarding blood cultures in children.¹¹³

Stool Culture

Indications

Most diarrheal illness is caused by viral pathogens, and most bacterial causes of diarrhea in children do not require antibiotic treatment. (In fact, in the case of *Escherichia coli* 0157:H7, antibiotics may be deleterious.) For this reason, bacterial cultures of the stool may be more important for reasons of public health and controlling outbreaks rather than for individual patient care. In 1 study of children under age 1 year with diarrhea, 3 clinical factors predicted a bacterial etiology:

1. History of blood in the stool (best individual predictor; sensitivity 39%, specificity 88%).
2. Temperature greater than 39.0°C (102.1°F) (sensitivity 34%, specificity 85%).
3. Occurrence of 10 or more bowel movements in a 24-hour period (sensitivity 28%, specificity 85%).¹¹⁴

Children who meet any 2 of these criteria are at greatest risk for bacterial enteritis; however, the isolated finding of visible blood in the stool will prompt many ED clinicians to order a stool culture.

Pros

Stool culture has high sensitivity and specificity for bacterial enteropathogens. For certain pathogens (eg, *Shigella*, *Campylobacter*), a positive culture should lead to prompt treatment and, it is hoped, earlier relief of symptoms. Successful treatment also reduces the risk of spread to uninfected contacts. The test is reasonably noninvasive and inexpensive.

Cons

Stool culture results are usually not available for 24 to 72 hours. More importantly, the pathogen cultured (eg, *Salmonella*, pathogenic *E. coli*) often does not require treatment nor does treatment provide any benefit.

Lumbar Puncture

Indications

Lumbar puncture is arguably the most important test in the evaluation of the febrile child. The child with no source of infection but who appears toxic despite a reduction in temperature requires lumbar puncture. Even the child with an obvious source of infection may need lumbar puncture if he or she appear toxic or has a stiff neck. As many as one-third of children with bacterial meningitis have a concurrent infection such as pneumonia, otitis media, or orbital cellulitis.¹¹⁵ Routine lumbar puncture is not necessary in the child with a simple febrile seizure who does not appear toxic and has no meningeal signs.^{116,117}

Prior use of antibiotics can affect the clinical presentation in meningitis and may lower the threshold for performing a lumbar puncture. In a retrospective study by Rothrock et al, children treated before diagnosis had lower temperatures, fewer alterations in mental status, and longer-lasting symptoms.¹¹⁸ These authors also found that children with meningitis who were already on an antibiotic at the time of diagnosis also had more frequent vomiting; more concurrent ear, nose, and throat infections; and more physician visits during the week before meningitis was detected when compared with children not on antibiotics. The incidence of upper respiratory symptoms, seizures, nuchal rigidity, Kernig and Brudzinski signs, focal neurologic signs, mortality, and length of hospitalization did not differ between the 2 groups of patients.

Pros

Lumbar puncture has extremely high sensitivity and specificity for the diagnosis of bacterial, as well as viral, meningitis. For bacterial meningitis, earlier diagnosis and prompt treatment should (at least theoretically) improve the prognosis by decreasing the risk of death or major morbidity, although 1 study has called this conjecture into question.¹¹⁹

Cons

Lumbar puncture is frightening to children and their parents, even with adequate local anesthesia, and is associated with moderate levels of pain and discomfort. Theoretically, the spinal needle used in the procedure could actually introduce meningeal infection, but the risk of such a complication appears to be extremely remote.³⁸

Some children may be too ill to undergo lumbar puncture. The moribund child may suffer respiratory failure or cerebral herniation during the procedure. One study has suggested that antibiotics be given and the lumbar puncture deferred until the patient's condition stabilizes for children who exhibit decerebrate or decorticate posturing or focal neurologic signs or who show no response to pain.¹²⁰

Treatment

Empiric Antibiotic Therapy

Perhaps no aspect of the management of the febrile child has been more controversial than the use of empiric ("expectant") antibiotic therapy in those with no documented bacterial infection. Both observational studies and randomized, controlled trials have examined the efficacy of empiric antibiotic treatment in reducing the risk of subsequent meningitis and other infectious complications in such cases, the results of which will now be described.

Results Of Observational Studies

Observational studies consistently report that fewer "new" foci of infection develop in children with bacteremia who were treated with antibiotics at the initial visit than in those who did not receive antibiotic therapy.^{38,111,121-127} One meta-analysis that uncritically pooled data from both observational studies and randomized trials reported that the risk of bacterial meningitis was significantly reduced among children with bacteremia treated with antibiotics at the initial visit.¹²⁸ But these studies were inherently biased toward finding a beneficial effect of treatment, because treatment was not assigned randomly. In particular, the studies were carried out primarily at academic tertiary care EDs and walk-in clinics. The vast majority of those children who initially received antibiotics were those in whom foci of bacterial infection, such as pneumonia or otitis media, had been identified. Because they already had a focal bacterial infection, the children who were treated were obviously at much lower risk for a new focus of infection. Most likely some of the untreated children had pneumonia, otitis media, or UTI that went unrecognized, so at follow-up, these pre-existing foci were classified as "new;" since these children were not initially treated with antibiotics, they were at risk for meningitis and other serious complications. The pneumonia or the UTI may not

have been recognized because the requisite diagnostic tests (chest radiograph or urinalysis and urine culture) were not performed. Otitis media is notoriously difficult to diagnose and may have escaped detection at the initial visit, particularly if the tympanic membrane was difficult to visualize or erythematous membranes were noted in a crying child.

Results Of Randomized, Controlled Trials

Clearly, randomized, controlled trials (RCTs) are more likely to yield a scientifically valid answer to the question of whether empiric antibiotic treatment is effective. Four such trials have been published^{108-110,129}; 2 involved oral antibiotics versus placebo (an initial dose of intramuscular benzathine penicillin was given in the study by Carroll et al),^{108,129} whereas the 2 other studies involved intramuscular ceftriaxone versus oral antibiotics (amoxicillin or amoxicillin/potassium clavulanate).^{109,110} Unfortunately, all 4 trials had substantial methodologic problems. In all, the statistical analyses were limited to children who later proved to have had bacteremia at the time they were enrolled (about 3% of the total). When the results are expressed in terms of all children randomized (the correct analysis for any randomized trial), no significant benefit was seen in terms of reducing the risk of subsequent bacterial meningitis. The presence or absence of bacteremia cannot be ascertained at the time of the initial visit, when the clinician must decide whether or not to treat, and thus the analysis should not be restricted to children with bacteremia. Such an analysis obviously ignores the outcomes in the 97% of children without bacteremia who were randomized and treated. Moreover, the majority of cases of bacterial meningitis that occurred in these trials were due to *H influenzae* type b (Hib), which has now

been virtually eliminated since the introduction of conjugate Hib vaccines.^{127,130,131} Finally, the authors of a meta-analysis of studies of occult *Streptococcus pneumoniae* bacteremia found that meningitis rarely developed (occurring in less than 3% of all the children with bacteremia) and that there was no significant decrease in the progression to meningitis among the children treated with antibiotics.^{132,133} Even if cases of meningitis could be prevented, the authors of this meta-analysis noted that in order to prevent 1 case of meningitis, more than 2500 febrile infants and children would have to undergo culture testing and treatment (presumably causing side effects in 200 to 500 cases).^{132,133}

The only outcome analyzed in these trials of empiric antibiotic treatment that appears to be of genuine benefit is more rapid defervescence. The shorter duration of fever in children treated empirically is probably explained by the presence of unrecognized focal bacterial infection (eg, pneumonia or otitis media) at the initial visit. Given the concern over selection for resistant organisms with the use of broad-spectrum antibiotics,¹³⁴⁻¹³⁸ this questionable benefit does not justify empiric treatment for the large number of young febrile children who have fever with no identifiable source.

The “Double Standard” And Pressure To Prescribe

The reliance on empiric treatment raises another important question: How can we justify the use of CBCs and blood cultures along with parenteral antibiotic treatment for the child with no focus of bacterial infection but not for the febrile child with an identifiable focus, such as otitis media or pneumonia? Blood culture results are positive at least as often in children with these latter conditions as in those without such a focus,^{124,125,139-141}

Practical Antibiotic Pearls

Keep the good stuff on hand.

- Stock the most important parenteral antibiotics in the ED (ceftriaxone or cefotaxime).

Set limits.

- If the child appears toxic, tell the nurse, “If antibiotics are not infusing in 15 minutes, come and get me!”

Get a dive watch.

- For those of you who do not SCUBA dive, a bezel is a ratcheted, numbered dial on a watch rim that keeps track of elapsed time. Every time you have a child with suspected meningitis or meningococemia, set the bezel for 15 minutes

— your personal antibiotic deadline. When 15 minutes pass, check to be sure the antibiotics are running.

Don't overdo it.

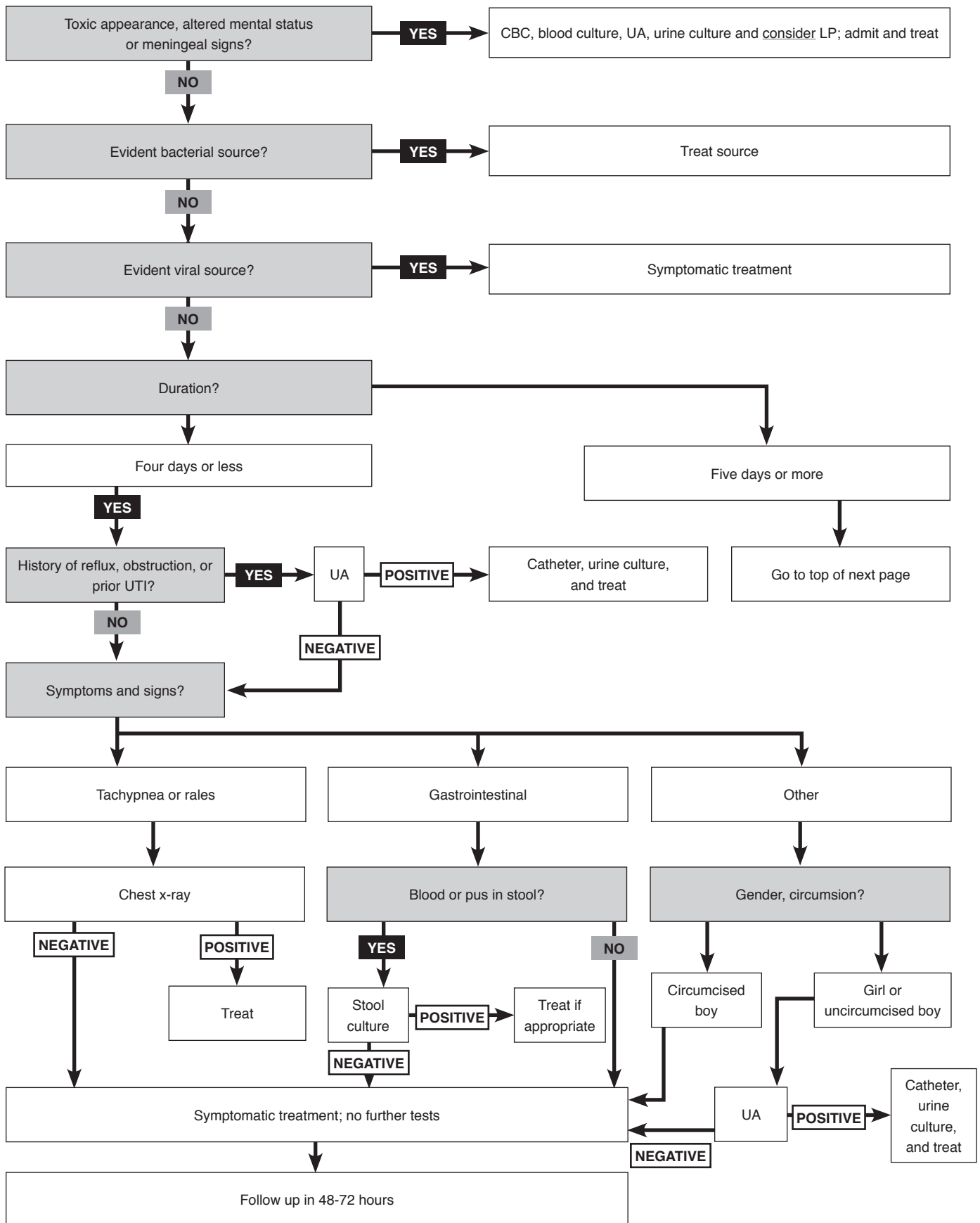
- No antibiotics or testing is needed in children under 2 with exudative tonsillitis. It is always a viral infection.

Go to the bone.

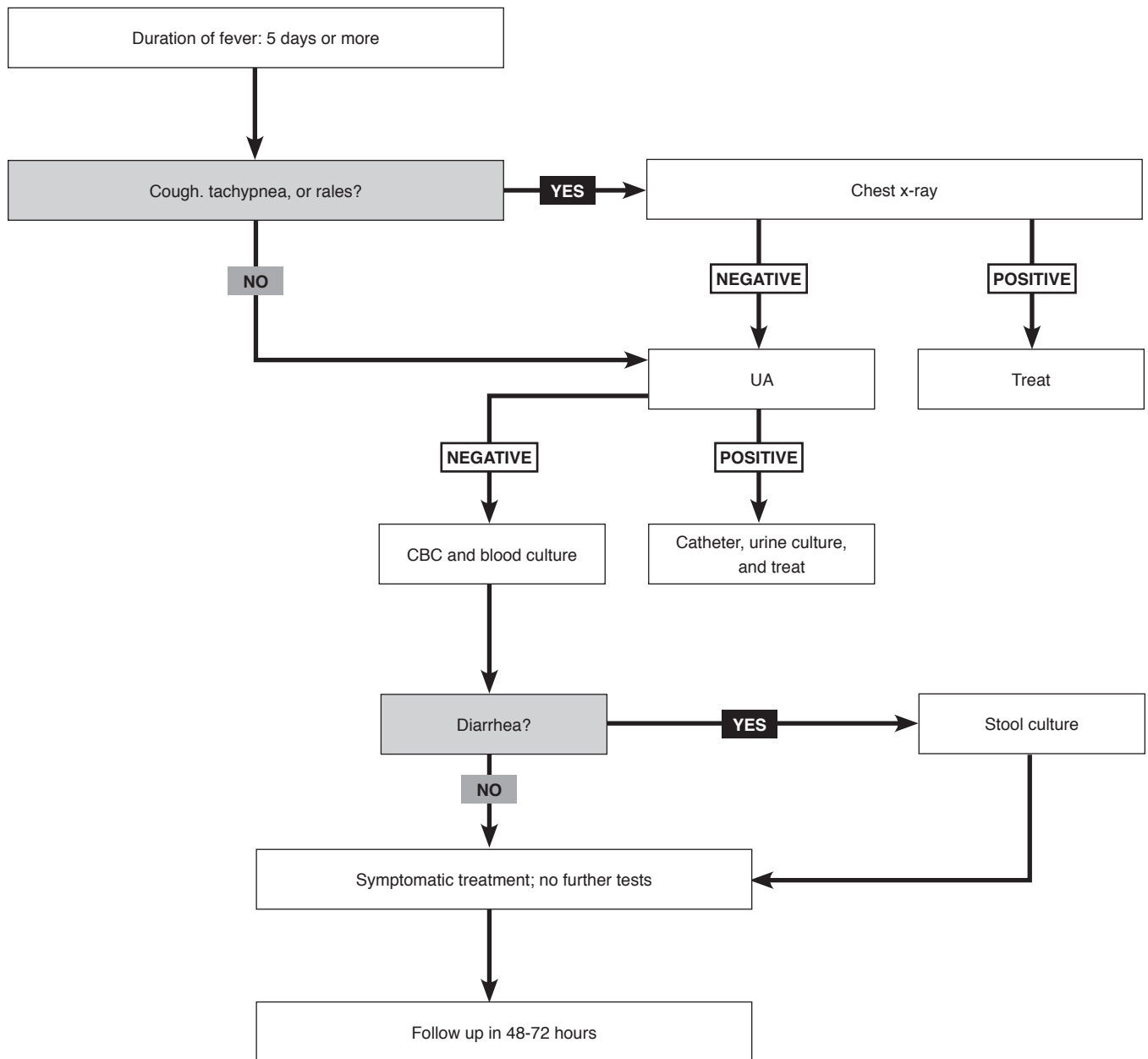
- A febrile, moribund child who needs antibiotics cannot wait 40 minutes for the IV team to start a line. If an IV cannot be started within several minutes, consider an intramuscular or even intraosseous dose of antibiotics.

Clinical Pathway For Management Of The Young Febrile Child

(continued on page 17)



Clinical Pathway For Management Of The Young Febrile Child (continued from page 16)



yet few clinicians even attempt to defend this “double standard.”

Finally, some parents expect antibiotics to be prescribed if their child has a fever, and they routinely pressure the clinician to provide a prescription (or even insist on it).¹⁴² Many physicians shamelessly prescribe antibiotics for viral infections and are still able to sleep at night. Over 40% prescribe antibiotics for the common cold.¹⁴³ Yet some physicians still have enough lingering self-respect to be embarrassed by such practices. Their solution to this dilemma of “antibiotic addiction” is a diagnosis of otitis media. Who’s to say the ear isn’t a little bit red? When the source of fever remains unclear, the clinician can bypass all the controversy regarding CBCs and blood cultures, write “otitis media” on the chart, and hand mom a script for amoxicillin. Case closed. (Not that readers of *Emergency Medicine Practice* have

ever done such a thing!) However, it is more scientific, honest, and honorable to search for a real focus of infection, including a UTI in the child with a high fever and equivocal ear findings. If antibiotics are not indicated, this should be explained to the parent. Some EDs supply parents with a preprinted handout from the CDC series Get Smart: Know When Antibiotics Work. (Available at <http://www.cdc.gov/getsmart/campaign-materials/onepage-sheets.html>)

Cold Medications

Parents may also inquire whether cold medications can be prescribed for their child if no bacterial source of fever can be found. However, in 2008, the Food and Drug Administration published a health advisory statement long-espoused by experts in the field: that children younger than 2 years should not

Cost-Effective Strategies For Managing The Febrile Child (continued on page 19)

1. No “shotgunning.”

The emergency clinician can be a medical “sniper” instead of a “shotgunner.” Zero in on your target with the history and physical. Perform a lumbar puncture or arthrocentesis when indicated. One positive lumbar puncture is worth more than a thousand “positive” CRPs, ESRs, or CBCs. Some consider performing these “inflammatory” tests as akin to blasting into the bushes in a vague hope of hitting some unseen, rapidly moving target. One recent ED study on febrile children examined the positive predictive values and likelihood ratios of laboratory tests. They could not accurately predict either serious bacterial disease or culture positivity.¹⁴⁷ The findings supported greater reliance on clinical impression and less on laboratory values.

Risk Management Caveat: Some laboratory tests are very important. These include urine cultures or dipstick urinalysis in the appropriate clinical situation. Analysis of the CSF and synovial fluid is of extreme importance in the toxic child or in those suspected of having a septic joint.

2. Use dipstick urinalysis versus microscopy in febrile child.

A clean-voided bag urine specimen is inadequate for culture because of an unacceptably high contamination rate.⁸⁴ It is probably sufficient for urinalysis, however. A dipstick urinalysis positive for leukocytes or nitrites is essentially as sensitive as a urine Gram stain (88% vs 93%). It is much faster and less expensive. In addition, urine dipstick is more sensitive for UTI than pyuria found

on microscopy.⁸² If the dipstick is positive for leukocytes or nitrites, a specimen should be obtained by catheterization or suprapubic aspiration and sent for culture.

Risk Management Caveat: Evidence suggests that pyelonephritis that remains untreated for 5 or more days is more likely to lead to renal scarring (and its potential sequelae).⁸⁸ (However, most lower-tract UTIs, if left untreated, appear to resolve spontaneously.¹⁴⁸) Obtain a urine culture in the high-risk child who has a fever and no source—that is, young white females, uncircumcised males—if the child is ill enough to receive empiric antibiotics, or has a history of prior UTI.

3. Limit the workup of febrile seizures.

Children with febrile seizures have no greater incidence of bacteremia than febrile children who do not seize. An extensive evaluation involving CBC, electrolytes, calcium, magnesium, CT, EEG, and LP is not necessary. If the child has a source of infection, simply treat it. If the child has no obvious source, consider urine culture in males under 6 months or females under 2 years old. Blood cultures may be helpful if follow-up is problematic.

Risk Management Caveat: Do a good history and physical exam. Determine that the child truly had a simple febrile seizure. They should be between the ages of 6 months and 6 years with a single, generalized (not focal) seizure lasting less than 10 minutes. They should not have had a prolonged postictal state. Most importantly, the

be given cold medications because of possible serious or even life-threatening side effects. Even more cautious recommendations have been put forth by the American Academy of Pediatrics: “Over-the-counter cough and cold medications do not work for children younger than 6 years and in some cases cause a health risk.”^{viii,ix} Clinicians are encouraged to assure parents that viral cold symptoms, although annoying and uncomfortable, are usually self-limiting.

Importance Of Follow-Up

The conscientious practitioner relies heavily on careful follow-up, since the appearance of new signs or symptoms will alter the diagnostic probabilities. The key to management is the clinical trajectory — is the child getting better or getting worse? Most

importantly, does the child who was only mildly ill now have signs compatible with meningitis? Finally, follow-up is valuable in assessing the parents’ ability to cope with a child who remains febrile or has other persistent symptoms.

ED clinicians often bemoan the lack of follow-up care, especially for the poor, the “doctorless,” the uninsured, and the patients seen on Friday night. But this attitude is foolish, since patients have access to an excellent follow-up system — the ED. If parents are in doubt about their child’s condition, they should bring febrile children back for a recheck. Reliable parents will return if their child becomes worse; those parents who seem less reliable can be told to return for a mandatory recheck the next day. An alternative to an actual visit is telephone contact with the parent. Some EDs maintain a call-back log in which the clinician writes the name and phone

Cost-Effective Strategies For Managing The Febrile Child (continued from page 18)

child should be interactive and not toxic upon examination. They should not have neurologic abnormalities or meningeal signs.

4. Limit blood cultures.

Besides the discomfort of the test, knowledge that the child who is found to have been bacteremic at the initial visit and who remains febrile for 24-48 hours often leads to additional diagnostic tests (repeat blood culture, LP), admission, and parenteral antibiotic therapy. For the vast majority of children who have already cleared their bacteremia spontaneously or will subsequently do so, these additional interventions are unnecessary.

Risk Management Caveat: Blood cultures should always be obtained in a child with fever and purpura, or with petechiae below the nipple line, and before initiating antibiotic treatment for suspected bacteremia, meningitis, septic arthritis, or osteomyelitis.

5. Limit chest radiographs.

Restrict chest radiographs to children with suggestive symptoms and signs (especially tachypnea and rales) or prolonged (≥ 5 days) fever with cough. Although “positive” chest films are sometimes seen in children without respiratory symptoms, it is unknown whether this occurs more commonly than in well, afebrile children or whether antibiotics are useful or necessary to “treat” the detected infiltrates.

Risk Management Caveat: Chest radiographs may be under-used in children with prolonged fever and persistent cough whose chest examination shows no tachypnea, rales, or other adventitial sounds.

6. Order a single-view chest film.

There is no need to obtain both a posterior-anterior (PA) and lateral chest film in the child suspected of pneumonia. The study may be safely limited to a single PA view.¹⁴⁹ Besides the cost of the additional film, routinely including a lateral view doubles the radiation exposure.

Risk Management Caveat: The lateral film may be helpful in patients with an unclear or non-diagnostic PA view, or when there is suspicion of cardiac or malignant disease.¹⁵⁰

7. Limit the use of broad-spectrum parenteral antibiotics.

Other than a high rate of defervescence at follow-up, broad-spectrum parenteral antibiotics have no proven benefit over narrow-spectrum oral agents like amoxicillin. Moreover, broad-spectrum agents increase selection pressures favoring antibiotic-resistant organisms, both in the patient and in the community.

Risk Management Caveat: Any child who appears ill enough to require hospital admission probably merits parenteral therapy, after a blood culture and LP have been obtained.

number of the person to be contacted, and a nurse is designated to make a follow-up call the next day. **Figure 1, Sample Discharge Instructions For The Child With Fever** can help ensure that the instructions parents or guardians receive will be remembered and followed. It has been noted, however, that in one-third of cases, the guardians of children who are discharged from the ED cannot be reached by telephone over the next 72 hours.¹⁴⁴ Some EDs then rely on telegrams to contact the patient guardian.

Summary

The Clinical Pathway For Management Of The Young Febrile Child (see pages 16-17) offers an algorithm based on the principles discussed in this issue. The ED clinician should first screen for children whose condition mandates specific management, such as those who appear toxic despite fever reduction or who have an altered mental status, meningeal signs, petechiae below the nipple line, or purpura. These children require a more extensive diagnostic

Risk Management Pitfalls For The Febrile Child

Most of these excuses have a common theme. If you are sued regarding your care of a febrile child, it will most likely be for 1 of 2 reasons — failure to diagnose meningitis or meningococemia, or failure to administer antibiotics in a timely fashion.

1. **“It was the nurse’s fault!”**

So you say it was the nurse’s fault that the antibiotics were not given until the child began posturing. A jury will have to decide that. But if you had set your bezel (watch dial showing elapsed time) and checked back with her, you would have discovered she had trouble starting the IV, getting the antibiotics from the pharmacy, and had “lots of other patients to take care of.”

2. **“I never even thought to get a urine test. Her urine did not smell, and mom said she was urinating normally.”**

Urine infections are an important cause of pediatric fever. Clinical findings are not helpful. Do the test.

3. **“Sickle cell?! The mom never told me her child had sickle cell! I would have given antibiotics and admitted him if I had known.”**

Sometimes you just have to ask. Children with immune suppression require extra care and more aggressive management strategies. Ask, “Does your child have any medical problems?” “Has she ever been in a hospital after she was born?” Amazingly, parents do not always volunteer important information.

4. **“I thought it was a viral exanthem. I never saw a case of meningococemia before.”**

That’s no excuse. Clinicians are expected to recognize the most aggressive and deadliest of pediatric diseases. When examining a febrile child with a rash, check to see (and document) whether the rash will blanch. You can even take a glass slide and press down on the skin to get

a real-time view of the blanching process in equivocal cases. A petechial rash, especially below the nipple line or in an ill-appearing child, means instant antibiotics. (Plus, children with Henoch-Schönlein purpura will not be adversely affected by 1 dose of ceftriaxone.)

5. **“I know he looked sick, but he really didn’t have clear-cut meningeal signs. I thought I would just continue the amoxicillin his pediatrician started 3 days before.”**

Children with partially treated meningitis may not have classic findings. If a child remains febrile for several days on antibiotics, has no obvious focus, and looks somewhat ill, he or she may need a lumbar puncture.

6. **“But she had otitis media! It even showed up on the autopsy.”**

One-third of children with meningitis have a concurrent extrameningeal infection. Toxic-appearing children, especially those with meningeal signs, need a lumbar puncture despite the presence of otitis media.

7. **“When I saw the child had a stiff neck, I called the pediatrician. He came in and did the lumbar puncture, and after we got the results, we gave the antibiotics. I haven’t done an LP on a child in years.”**

In litigation, it is not the issue of “if” antibiotics but “when.” Some textbooks suggest that antibiotics be given within 30 minutes after meningitis becomes a reasonable suspect. The plaintiff’s bar has guidelines for antibiotic administration as well: their general rule is that antibiotics should always be given at least 30 minutes before they actually were!

There is no need to defer antibiotics if the lumbar puncture will be delayed. Cultures will be positive for hours after administration; pleocytosis and antigens, for days.

work-up, empiric antibiotic treatment, and admission to the hospital. Altered mental status or meningeal signs, even in the absence of overt toxicity, mandate lumbar puncture.

Clinically evident bacterial infections require appropriate antibiotic therapy, whereas clinically identifiable viral infections may benefit from symptomatic treatment (eg, antipyretic agents, or topical or systemic antipruritic agents).

When obtaining the patient history, the ED clinician should focus on the duration of fever and determine whether it is continuous or intermittent. Associated symptoms are often helpful in increasing or decreasing the value of specific diagnostic tests (eg, a chest radiograph in a child with a high fever and persistent cough, or a stool culture in a child with bloody or purulent diarrhea). Gender, circumcision status, and previous history of UTI are useful information in deciding whether to perform a urinalysis.

The physical examination is most helpful in

eliciting meningeal signs and respiratory signs suggestive of pneumonia (rales, tubular breath sounds, tachypnea). The latter suggest the need for a chest radiograph. Wheezing, reduced or asymmetric air entry, and/or retractions may prompt a trial of inhaled bronchodilators.

The decision to draw blood for a CBC or blood cultures in a febrile child with a temperature above 39.2°C (102.5°F) and no identifiable source of infection does not represent the standard of care. ED clinicians routinely ignore practice parameters that suggest such an approach.^{12,14,145} Most parents feel that the “blood test”-based strategy is generally too aggressive. They would prefer fewer painful tests and procedures, shorter stays in the ED, and lower costs,¹⁴⁶ and they are glad to return for a re-evaluation if the child’s condition deteriorates.

Future research may well suggest changes in either diagnostic or therapeutic management. In particular, new rapid diagnostic tests may lead to early detection and treatment of occult bacterial infections.

Figure 1. Sample Discharge Instructions For The Child With Fever

Return to the Emergency Department if your child:

- Becomes more fussy or won't stop crying
- Gets too sleepy or drowsy
- Gets a stiff neck
- Won't stop vomiting
- Gets a new rash
- Has a seizure
- Gets any other new or worsening symptom(s) that concerns you

Follow-up

- See Dr. _____ within _____
- Call _____ for appointment
- Return here for a recheck in _____

What to do:

- If your child is prescribed an antibiotic, be sure to finish all of the antibiotic. Do not stop the medicine, even if your child is feeling better. Taking all of the antibiotic will help keep the infection from returning.
- Give your child acetaminophen (Tylenol®) or ibuprofen (Children's Advil®/Motrin®) for fever or pain.
- Do not give aspirin.
- Do not sponge your child with alcohol.

Acetaminophen Dosing

Age (Weight)	Infant Drops (80 mg/0.8 mL)	Children's Elixir (160 mg/5 ml)	Children's Tablets (80 mg/tablet)	Junior-Strength (160 mg/caplet)
0-3 months (6-11 lbs.)	1/2 dropper (0.4 mL)	—	—	—
4-11 months (12-17 lbs.)	1 dropper (0.8 mL)	1/2 tsp.	—	—
12-23 months (18-23 lbs.)	1.5 droppers (1.2 mL)	3/4 tsp.	—	—
2-3 years (24-35 lbs.)	2 droppers (1.6 mL)	1 tsp.	2 tablets	—
4-5 years (36-47 lbs.)	—	1.5 tsp.	3 tablets	—
6-8 years (48-59 lbs.)	—	2 tsp.	4 tablets	2 caplets
9-10 years (60-71 lbs.)	—	2.5 tsp.	5 tablets	2.5 caplets
11 years (72-95 lbs.)	—	3 tsp.	6 tablets	3 caplets
12-14 years (96 lbs. and up)	—	—	—	4 caplets

Remember that the emergency department is open 24 hours a day, every day, and we are always glad to see you.

The introduction of conjugate pneumococcal vaccines should reduce the febrile child's risk of occult pneumococcal bacteremia and of pneumococcal meningitis. Furthermore, if this vaccine proves more than 95% effective, the incidence of bacterial pneumonia will fall dramatically, from about 20% to less than 2% to 3% of all cases of pneumonia in infants under 3 years of age. In the meantime, the proposed algorithm should help both office-based and ED clinicians to identify those infants and young children who require diagnostic testing, to avoid unproven and potentially harmful treatments, and to ensure adequate follow-up of children whose fever persists.

After having read this issue of *Emergency Medicine Practice*, you may never perform another CBC in a febrile child yet still deliver stellar care — as long as you stick enough needles in the L2–3 interspace and ensure adequate follow-up.

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David McGillivray, MD and Martin Pusic, MD provided valuable comments and suggestions on a previous version of this manuscript.

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Evidence-based medicine requires a critical appraisal of the literature based upon study methodology and number of subjects. Not all references are equally robust. The findings of a large, prospective, randomized, and blinded trial should carry more weight than does a case report.

To help the reader determine the strength of each reference, pertinent information about the study (such as type of study and number of patients) is included, when available, in bold type following the reference. In addition, the most informative references, as judged by the author, are tagged with an asterisk (*) next to the number of the reference.

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The following new references have been added by the editor for this revised version.

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- viii. <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2008/ucm116964.htm>. (Policy statement)
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CME Questions

1. Which of the following viral infections is not characterized by rash?
 - a. Varicella
 - b. Measles
 - c. Croup
 - d. Herpes simplex gingivostomatitis
2. Sources of occult bacteremia include all of the following EXCEPT:
 - a. Roseola
 - b. UTI
 - c. Pneumonia
 - d. Septic arthritis/osteomyelitis
 - e. Meningitis
3. *H influenzae* type b:
 - a. Has increased significantly in recent years
 - b. Has virtually disappeared due to the widespread use of the Hib vaccine
 - c. Is frequently the cause of otitis media
 - d. Occurs much more frequently in summer than winter
4. A higher risk of UTI occurs with all of the following EXCEPT:
 - a. Males under 6 months of age
 - b. Females under 2 years
 - c. Those with uretero-vesicle reflux
 - d. Uncircumcised males
 - e. Black children

5. **A history of reduced appetite and activity in the febrile child:**
 - a. Is not helpful in developing a differential diagnosis
 - b. Is suggestive of meningitis
 - c. Increases the probability of UTI
 - d. Is seen primarily in viral vs. bacterial infection

6. **All of the following suggest meningitis in the febrile child EXCEPT:**
 - a. High Yale Observation Scale score
 - b. Kerning's sign
 - c. Braham's sign
 - d. Bulging fontanelle

7. **Important historical considerations in the febrile child up to 3 years old include:**
 - a. Whether the child has seen another doctor in the past week
 - b. Whether the child has taken any prescribed or non-prescribed antibiotics recently
 - c. Travel history and day care attendance
 - d. Prior infections, especially UTIs and pneumonia
 - e. All of the above

8. **All of the following have important diagnostic implications EXCEPT:**
 - a. Especially high fevers
 - b. General appearance
 - c. Response to antipyretics
 - d. Past medical history

9. **The Yale Observation Scale score:**
 - a. Can be used to assess a child's risk for serious illness
 - b. Is significantly higher in children with meningitis
 - c. Is based on the child's cry, wakefulness, color, hydration, and response to parents and social overtures
 - d. All of the above

10. **Which of the following most strongly suggests otitis media?**
 - a. Decreased mobility of the tympanic membrane
 - b. Red ears
 - c. A child who pulls or tugs at his or her ears
 - d. Lack of other clinical diagnosis in the febrile child

11. **The diagnostic test least likely to lead to a clinically beneficial change in treatment strategy is:**
 - a. The CBC
 - b. Lumbar puncture
 - c. Urinalysis
 - d. Chest x-ray

12. **The CBC:**
 - a. Can distinguish between *N meningitidis* bacteremia and viral illness
 - b. Shows a leukocyte count of more than 15,000/cc³ in the majority of children with bacterial meningitis
 - c. Can determine the need for lumbar puncture
 - d. Is associated with high false-positive and false-negative rates

13. **Urinalysis and urine culture:**
 - a. Are less valuable than urine odor, urinary frequency, and dysuria in establishing a diagnosis of UTI
 - b. Are generally recommended in females younger than 2 years old and males younger than 6 months who have fever and no source
 - c. Are correlated with a very high false-positive rate for UTI
 - d. Result in many complications if obtained by a catheter

14. **Indications for chest x-ray in febrile children older than 3 months include all of the following EXCEPT:**
 - a. Respirations of 50/min or higher
 - b. Nasal flaring, retractions, and grunting
 - c. Diminished breath sounds
 - d. Rales
 - e. Isolated cough

15. **Lumbar puncture:**
 - a. Is indicated in children with no source of infection who appear toxic despite temperature reduction
 - b. Is indicated in all children with febrile seizures
 - c. Is never necessary in cases of prior antibiotic use
 - d. Does not occur in conjunction with otitis media

16. **Empiric antibiotic treatment:**
 - a. Causes no side effects
 - b. Is universally supported in the literature
 - c. May result in allergic reactions, diarrhea, or serum sickness
 - d. Is indicated for treatment of the common cold

Pharyngitis In The ED: Diagnostic Challenges And Management Dilemmas

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CME Objectives

Upon completing this article, you should be able to:

1. Discuss how the history and physical examination can identify causes of pharyngitis or determine the need for diagnostic testing, and how clinical decision rules may aid in this process.
2. Discuss the utility and limitations of different diagnostic studies used in evaluating patients with pharyngitis.
3. Discuss the identification and management of serious and/or potentially life-threatening causes of pharyngitis.
4. Describe how to identify and manage GABHS in adults and children.
5. Describe appropriate treatment, such as antibiotic therapy and/or pain management, for patients with pharyngitis.

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9:15 a.m.: It's an unusually slow day in the ED. As you pick up the chart of the only patient awaiting care, you smile. The chief complaint is "sore throat and rash," and the patient is an 11-year-old girl. Shortly after entering the room, however, you aren't smiling.

The girl is well-appearing except for a diffuse morbiliform rash. From her mother (who is standing in the corner with her arms folded, looking unhappy), you learn that one of your colleagues saw the child a few days ago and prescribed an antibiotic to treat her sore throat. She says in no uncertain terms, "My daughter's throat is still sore, and now she has this rash. I want the right antibiotic, and I want this rash gone!" You notice that she's holding a copy of the hospital's patient satisfaction survey in her hand.

Rarely is the complaint of sore throat a show-stopper that requires immediate action. Except for a handful of unusual but potentially life-threatening causes of pharyngitis, the ED clinician is principally concerned with identifying and treating patients who have "strep throat" — ie, infection with group A beta-hemolytic *Streptococcus* (GABHS) — to prevent a few rare but serious complications.

Effectively treating sore throat pain, ensuring adequate hydration, and promptly administering antibiotics when indicated will generally reduce or eliminate the patient's risk of long-term sequelae. Even so, the management of this "simple" condition is fraught with controversy and potential peril.

In this article we present an evidence-based approach to the evaluation and management of acute pharyngitis in adults and children. Emphasis is placed on accurately identifying and treating life-threatening causes of pharyngitis. In addition, options for managing the common causes of pharyngitis are described, including strategies to alleviate pain and discomfort, shorten the disease course, slow the rate of transmission, prevent complications

(such as acute rheumatic fever and peritonsillar abscess), and minimize the adverse effects of inappropriate antibiotic treatment.

Critical Appraisal Of The Literature

There is no dearth of information in the medical literature regarding the evaluation and management of the patient with pharyngitis. Even if we disregard industry-sponsored studies that compare different antibiotics, a veritable mountain of information remains. ED clinicians must understand the limitations of the medical literature in order to use it effectively as a guide in their practice. For example, virtually every study of diagnosis uses the throat culture on sheep's blood agar as the reference standard. However, a patient with viral pharyngitis may have a positive throat culture if he or she is a streptococcal carrier, and a patient with a true GABHS infection may have a negative throat culture if the specimen was not collected or incubated properly. Likewise, the true test of the effectiveness of a treatment for GABHS infections in pharyngitis is not whether the patient recovers from the acute episode but whether the therapy prevented serious poststreptococcal complications. The acute disease is self-limited; treated or not, the vast majority of patients will get better. Moreover, the complications are so rare that a study of their prevention is impractical, if not impossible. Given that the reference standard is flawed and the outcome to be achieved is somewhat unclear, it's no surprise to find that ED clinicians employ a wide range of diagnostic and treatment strategies.

Guidelines

Several groups, including specialty societies and respected academic entities, have issued practice

guidelines for the evaluation and management of pharyngitis. **Table 1** summarizes the most important guidelines. The Infectious Diseases Society of America (IDSA) produced an early set of guidelines, which were updated in 2002.^{1,2} Another revision is scheduled for spring 2010.¹ Guidelines have also been released by the American Academy of Pediatrics,³ the University of Michigan Health System,⁴ the Scottish Intercollegiate Guidelines Network,⁵ and the Centers for Disease Control and Prevention (CDC). The CDC document, which was endorsed by the American Academy of Family Physicians and the American College of Physicians–American Society of Internal Medicine (ACP-ASIM),⁶ has been published in the *Annals of Emergency Medicine* and may represent accepted care among ED clinicians.

All guidelines rely on a combination of scientific evidence and expert consensus, but, as one might expect, some offer conflicting advice. Several provide a range of acceptable options. Although these guidelines disagree about certain key issues, there is

general agreement on several fundamental issues:

- First, all the guidelines agree that patients with signs of viral illness can be managed symptomatically without testing or treatment. Conjunctivitis, cough, rhinorrhea, skin rash (other than scarlet fever, or scarlatina), and mucosal ulcers are all signs that the causative agent is likely to be a virus. When these signs are found in association with a sore throat, the guidelines agree on providing therapy to reduce the patient’s symptoms without testing for GABHS and without prescribing antibiotics.
- Second, the guidelines generally agree that the consequences of overlooking GABHS infection are not as serious for adults as they are for children. Therefore, a high-sensitivity rapid antigen detection test (RADT) is adequate for excluding this infection in adult patients, and a confirmatory culture is not necessary.
- Third, most of the guidelines agree that RADTs are not subject to false-positive results. A positive RADT will confirm the diagnosis of GABHS

Table 1. Summary Of Clinical Guidelines Pertaining To Pharyngitis

Organization	Population	Patients With Viral Symptoms	Patients With Symptoms of GABHS	Culture After Negative RADT?	Recommended Antibiotic
Infectious Diseases Society of America	Adults and children	Do not test or treat	RADT or culture; treat only those with positive results	Children: yes Adults: no	Penicillin Azithromycin or narrow-spectrum cephalosporin (eg cephalexin) if penicillin-allergic ⁱⁱ
Centers for Disease Control and Prevention (endorsed by the American Academy of Family Physicians and the American College of Physicians–American Society of Internal Medicine)	Adults (patients older than 15 years of age)	Do not test or treat	Use Centor criteria:* Centor score = 4: perform RADT or treat presumptively Centor score = 3: perform RADT or treat presumptively Centor score = 2: perform RADT or do not test or treat Centor score = 1 or 0: do not test or treat In all cases in which a RADT is performed, only those with positive results are treated	No	Penicillin Azithromycin or narrow-spectrum cephalosporin (eg cephalexin) if penicillin-allergic ⁱⁱ
American Academy of Pediatrics	Children	Do not test or treat	RADT or culture; treat only patients with positive results	Yes	Penicillin Azithromycin or narrow-spectrum cephalosporin (eg cephalexin) if penicillin-allergic ⁱⁱ
Institute for Clinical System Improvement	Adults and children	Do not test or treat	RADT or culture; treat only patients with positive results	Yes	Penicillin Azithromycin or narrow-spectrum cephalosporin (eg cephalexin) if penicillin-allergic ⁱⁱ

* Centor criteria: history of fever; absence of cough; swollen, tender, anterior cervical lymph nodes; and tonsillar exudate.

Sources: Bisno AL, Gerber MA, Gwaltney JM, et al. Practice guidelines for the diagnosis and management of group A streptococcal pharyngitis. *Clin Infect Dis*. 2002;35:113-125; Schwartz BM, Marcy MS, Phillips WR, et al. Pharyngitis—principles of judicious use of antimicrobial agents. *Pediatrics*. 1998;101:171-174; Cooper RJ, Hoffman JR, Bartlett JG, et al. Principles of appropriate antibiotic use for acute pharyngitis in adults: Background. *Ann Emerg Med*. 2001;37:711-719.

pharyngitis, and treatment can begin without further testing.

- Finally, the guidelines all agree that penicillin remains the drug of choice for the treatment of GABHS infection, with erythromycin and azithromycin being reserved for those who are penicillin-allergic. We recommend azithromycin because it has the benefit of requiring a shorter treatment course and a better safety profile relative to erythromycin.^{iii,iv} Many of the guidelines also recognize that amoxicillin, taken once or twice a day, may represent a more palatable and convenient alternative, but further study may be needed to confirm its comparable efficacy.

Evidence-Based Reviews

The most significant evidence-based review appeared in the Cochrane database in 2000⁷ and was updated in 2008.^v In this critical appraisal of the literature, the reviewers considered 27 studies and 12,835 cases of sore throat, specifically to determine whether antibiotic treatment confers any immediate or subsequent benefit. (The reviewers did not consider diagnostic strategies.) Studies were selected using the following criteria:

1. They involved patients with acute sore throat who presented to primary care practitioners. Both adults and children were included.
2. The outcome measures included the presence or absence of poststreptococcal complications (eg, rheumatic fever, glomerulonephritis, or peritonsillar abscess) and the resolution of symptoms (eg, sore throat, fever, or headache).
3. The studies were randomized or “quasi-randomized” placebo-controlled trials.

The Cochrane review concluded that antibiotic treatment does indeed benefit specific subsets of patients and thus offers significant benefit to a minority even if it is at the cost of unnecessarily treating a substantial majority.

Epidemiology, Etiology, Pathophysiology, And Differential Diagnosis

Acute pharyngitis accounts for 1% to 2% of all visits to physician’s offices, clinics, and EDs.⁸ In practice, this translates to approximately 27 million visits each year, making sore throat a common complaint for both office-based practitioners and ED clinicians. Interestingly, it has been estimated that for each person who seeks care because of a sore throat, an additional 4 to 6 symptomatic individuals do not.⁷

Although most cases of pharyngitis are not dangerous and therefore do not require urgent care, the astute ED clinician will remember that a sore throat can be the presenting complaint for some serious and even immediately life-threatening illnesses.

Serious and/or potentially life-threatening causes include epiglottitis, diphtheria, Ludwig’s angina, peritonsillar abscess, retropharyngeal abscess, gonococcal pharyngitis, infectious mononucleosis (if tonsils and lymphoid tissues become enlarged enough to cause airway obstruction), and GABHS infection (the complications of which can include serious illnesses such as rheumatic fever). Less serious and usually self-limited causes include viral pharyngitis, non-GABHS bacterial pharyngitis, and candidiasis.

Non-infectious causes of pharyngitis include laryngeal/pharyngeal trauma, gastroesophageal reflux disease, persistent cough or postnasal drainage, thyroiditis, and malignancies.

Rare But Dangerous Causes Of Pharyngitis Epiglottitis

Two decades ago, ED clinicians and pediatricians were alert for the signs of acute epiglottitis in young patients. Although this disease has several potential causes, the most frequent by far is infection with *Haemophilus influenzae* type B (Hib). This invasive, encapsulated gram-negative coccobacillus is spread via respiratory droplets.⁹ Thanks to widespread immunization against Hib, epiglottitis is now very rare among children in the developed world. Still, it does occur at a reported rate of 1 case per 100,000 people per year among adolescents and adults. Hib might not be the most common cause of epiglottitis in this population, but some have postulated that it causes the most severe cases.¹⁰⁻¹⁷

The presenting signs among children are often dramatic and may include drooling, dysphonia, and inspiratory stridor.^{14,15} Fever is followed within a few hours by symptoms of respiratory distress. While Hib vaccination (recommended by the World Health Organization and CDC to be given starting after the age of 6 weeks) succeeded in reducing the incidence of epiglottitis, several recent epidemiologic studies have indicated a resurgence of this illness, which can present in various forms, such as pneumonia or meningitis. Thus, global vaccination strategies may need to be reevaluated.^{vi}

Although adult patients can also arrive in the ED with fever of acute onset and acute airway obstruction, most will present less dramatically. In many cases the patient will report only intense pharyngitis and hoarseness. Other symptoms may include odynophagia and mild respiratory distress; drooling and stridor occur in more severe cases. Unlike the pediatric patient, the adult with epiglottitis may not be febrile and may have been symptomatic for several days rather than a few hours.

The ED clinician should be especially concerned if the patient has intense throat pain but little inflammation of the tonsils and hypopharynx. Dyspnea at the time of admission has been reported to be an important sign of potential airway obstruction.¹⁵⁻¹⁷

Diphtheria

Immunization has also virtually eradicated infections due to *Corynebacterium diphtheriae* in the United States. Diphtheria is caused by a gram-positive bacillus and is generally spread through respiratory droplets or contact with infected secretions. The most recent severe outbreaks have occurred in the former Soviet Union, where case-fatality rates have been as high as 23%.^{21,22} Unimmunized and immunocompromised children and adults continue to be at risk for both epiglottitis and diphtheria, and some evidence suggests that certain immunizations (including the Hib vaccine) are less effective in children who are HIV-positive. It is especially important to consider these infections when evaluating unimmunized or underimmunized patients such as immigrants from countries that lack large-scale immunization programs.²³

Ludwig's Angina

Originally described in 1836, Ludwig's angina is an infection of the submandibular and sublingual spaces. It is known to occur in both adults and children.^{18,19} In addition to fever, patients with Ludwig's angina present with a variety of complaints related to the oropharynx. Patients may have mouth, neck, or tooth pain or may report dysphonia, odynophagia, limited mouth-opening (trismus), and/or drooling.^{22,23} Dental disease, particularly of the mandibular molars, is the most common predisposing factor. Poor dental hygiene, recent dental treatment, local trauma, immunocompromise, and tongue piercing have been implicated as well. Ludwig's angina may also occur without any predisposing factors.^{23,24}

Peritonsillar Abscess

Peritonsillar abscess is typically an infection seen in older children and adolescents, although it can occur at any age. The abscess forms in the area between the palatine tonsil and the tonsillar capsule. It is the most serious expression of tonsillitis and, with an incidence of approximately 45,000 cases per year, is one of the most common significant head and neck infections found in either adults or children.²⁵ Most of these infections are polymicrobial and include both aerobes (eg, GABHS) and anaerobes (eg, *Fusobacterium*).

Peritonsillar abscess generally begins with pharyngitis. Over a period of 24 to 72 hours, the pain worsens and localizes to 1 side. The patient may have fever and complain of dysphagia, odynophagia, and ear pain. In severe cases drooling or dysphonia may be noted. Trismus is common and may also affect speech.²⁶ Peritonsillar abscess can be readily identified on physical examination. Those affected often have unilateral tonsillar enlargement with displacement of the tonsil (and often the uvula as well) to the contralateral side. In cooperative pa-

tients, the clinician may be able to palpate a fluctuant mass around the tonsil.

Retropharyngeal Abscess

The retropharyngeal space lies anterior to the prevertebral layer of deep cervical fascia and posterior to the pharyngeal mucosa. It is, in fact, not 1 but 3 potential spaces separated by fascia. These spaces extend from the upper pharynx to the mediastinum. In young children, the retropharyngeal space contains a large plexus of lymph nodes. Suppuration of these nodes allows infection to spread throughout the retropharyngeal space. As the child ages, the retropharyngeal lymph nodes involute and may become clinically insignificant as early as 3 or 4 years of age.²⁷ As a result, most of those affected tend to be very young children. Adolescents and adults can develop retropharyngeal abscesses, but these generally result from penetration of the posterior pharyngeal wall by a foreign object (eg, toothpick, fishbone).²⁸

Typically, the patient will present with fever, throat pain, and difficulty eating. Because this disease process develops more slowly than epiglottitis, patients are less likely to present with symptoms of abrupt onset. In fact, some patients will already have seen a physician prior to their ED visit and are taking antibiotics. Many patients also complain of neck pain and/or stiffness, the combination of which may lead the clinician to consider meningitis.^{27,29} Most patients lack the pharyngeal inflammation often seen in viral and bacterial pharyngitis; instead, the ED clinician may note asymmetry of the palate at the location of the abscess.

Infectious Mononucleosis

Infectious mononucleosis is caused by the Epstein-Barr virus (EBV), a member of the herpesvirus family. In underdeveloped areas, most of the population is infected with EBV during childhood, when the disease is asymptomatic. In developed nations, however, the disease often occurs in adolescents and young adults. Because of its ready transmission in bodily fluids, especially saliva, it has been dubbed "the kissing disease."

The classic triad of symptoms includes fever, sore throat, and lymphadenopathy. Tonsillopharyngitis, the most common symptom, occurs in 74% to 83% of patients.³⁰ Exudative pharyngitis is seen less frequently.

In practice it may be difficult for the ED clinician to distinguish infectious mononucleosis from other causes of pharyngitis. However, the course of the illness has some unique characteristics. Most patients experience 24 to 48 hours of malaise followed by fever; they may arrive at the ED after symptoms have been present for a week or more. Typically, the sore throat begins on days 3 to 5, progressively worsens over the next few days, and then gradually

improves.³⁰ On occasion, significant lymphadenopathy and tonsillar hypertrophy will develop. In some cases, these conditions may lead to upper airway obstruction.³¹ Splenomegaly, although not as common as other symptoms, supports the diagnosis of infectious mononucleosis, so the ED clinician should determine whether the spleen is enlarged.^{32,33}

HIV Infection

ED clinicians should also be aware that pharyngitis could be the initial presentation of acute infection with the human immune deficiency virus (HIV) and is part of the constellation of symptoms often described as “acute retroviral syndrome.” A nonexudative pharyngitis occurs in 50% to 70% of all patients with HIV infection. Fever, on the other hand, occurs in almost 100% of patients. Other accompanying symptoms include lymphadenopathy, maculopapular rash, myalgia, arthralgias, and mucocutaneous ulcerations. The ulcerations are typically seen on the tongue and floor of the mouth, but the tonsils and pharynx may also be involved.^{vii} Clinicians should recognize that routine screening and testing for HIV infection has become the standard of care in the ED in recent years and should be offered to patients at risk.^{viii}

For a more in-depth review of the literature on HIV infection as it is seen in the ED, see Chapter 3, “HIV-Related Illnesses: The Challenge Of ED Management.”

Common And Usually Less Dangerous Causes Of Pharyngitis

Patients who lack symptoms of airway obstruction and other serious signs nonetheless present a diagnostic and therapeutic challenge. In most cases, the underlying cause of the patient’s symptoms is an infection. The infectious agent usually causes symptoms by directly invading the pharyngeal tissue, and the ensuing immune response and release of inflammatory mediators cause further local inflammation.

Most cases of acute pharyngitis are self-limited. Treatment may have little or no influence on the course of acute bacterial pharyngitis and will have no influence whatsoever on the course of viral pharyngitis.³⁴ Because timely antibiotic treatment may prevent serious poststreptococcal complications, the ED management of infectious pharyngitis usually involves distinguishing between GABHS and non-GABHS causes. Diagnosis and treatment strategies remain controversial but are inextricably linked. For example, should a clinician choose to treat all patients with pharyngitis with antibiotics, then bacteriologic diagnosis becomes little more than an exercise in epidemiology. On the other hand, the clinician who aims to limit antibiotic therapy might choose a strategy that accurately identifies the organism before treatment begins. Such decision-making has been the object of much research and debate.

GABHS Infections

GABHS infections are significant because they are associated with nonsuppurative complications — specifically, rheumatic fever and poststreptococcal glomerulonephritis — but they are also associated with suppurative complications (eg, peritonsillar abscesses).

The incidence of GABHS varies widely within the population. Roughly 5% to 15% of adults with sore throats will have an infection caused by GABHS.³⁵⁻³⁷ In children, especially school-age children, the incidence of GABHS infection increases to 15% to 30%, with some authors suggesting that this figure may approach 50%.^{3,38,39} The incidence of GABHS in children under 3 years of age is generally reported to be much lower than it is in school-age children; although the matter is controversial, some believe that the incidence among these patients is comparable to that found in their older peers.^{39,40} Regional variations in the incidence have also been reported.^{37,41,42}

A certain number of patients are actually asymptomatic carriers of GABHS. Like the disease itself, the carriage rate varies with age and geographic location. Throat cultures obtained from carriers are likely to reveal GABHS, yet an actual GABHS infection in these patients is highly unlikely.^{37,41}

Non-GABHS Infections

Although GABHS is the most important cause of infectious pharyngitis, a sore throat is more likely to be caused by a virus than by GABHS, even among school-age children.^{42,43} A variety of other bacterial and viral agents have been described.

Other Bacterial Causes

Group C and Group G streptococci: Group C and Group G streptococci are the second and third most common bacterial causes of exudative pharyngitis after GABHS. Group C is more common in adolescents and young adults. The pharyngitis caused by this organism is less severe than that caused by GABHS. Group G streptococci have been implicated in “mini-epidemics” and in association with food-borne outbreaks (eg, ingestion of cold hard-boiled eggs).^{44,45}

Arcanobacterium haemolyticum: *A haemolyticum* is an interesting organism that can be either gram-positive or gram-negative, depending on when it is stained. The typical patient is an adolescent or young adult, but outbreaks of *A haemolyticum* infection have occurred in military barracks. Most patients have exudative pharyngitis and tender anterior cervical lymph nodes. However, unlike GABHS, many patients report pruritus and have a nonproductive cough. One- to two-thirds of patients with *A haemolyticum* infections develop a nonpeeling, scarlatiniform rash, which initially appears on extensor surfaces 1 to 4 days

after the onset of pharyngitis and then spreads to the trunk.⁴⁴⁻⁴⁶

Anaerobes: The 3 anaerobic organisms most frequently associated with pharyngitis are *Fusobacterium*, *Peptostreptococcus*, and *Bacteroides*. Anaerobes are associated with 2 entities: the first, and most important, is peritonsillar abscess; the second, and potentially more serious, are anaerobic infections that tend to occur in malnourished or immunosuppressed patients and in those who have undergone local irradiation of the neck. Affected individuals present with severe throat pain and foul breath odor. On examination, they are found to have purulent membranous exudates.⁴⁵

Neisseria gonorrhoeae: *N gonorrhoeae* infection is spread to the pharynx by orogenital contact. Male-to-female transmission is 2 to 3 times more common than female-to-male transmission. Homosexual men have the highest infection rates. Although most infections are asymptomatic, in some cases patients will experience mild pharyngitis with cervical lymphadenopathy. A concomitant sexually transmitted disease should lead the ED clinician to suspect *N gonorrhoeae*.^{44,45,47} Studies have shown that the failure to screen for this organism often leads to missed treatment opportunities; adolescents are especially at risk, and their failure to follow up highlights the importance of screening in the ED.^{ix}

Diphtheria: Thanks to widespread immunization, infection with *Corynebacterium diphtheriae* is exceptionally rare in most of the developed world, although there have been recent outbreaks in parts of the former Soviet Union. The characteristic gray or gray-brown pseudomembrane is the clinical finding that distinguishes diphtheria from other causes of pharyngitis. Although the pseudomembrane can cause airway compromise, the morbidity and mortality associated with diphtheria is primarily related to the cardiac and nerve toxins produced by the bacteria. The presence of the pseudomembrane and the associated clinical findings are generally sufficient to warrant the initiation of treatment with diphtheria antitoxin and penicillin or erythromycin. However, a culture of the pseudomembrane should be performed on tellurite selective media or Loeffler's media.^{19,44,45}

Atypical organisms: The role of *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* in pharyngitis is unclear. Chlamydial pharyngitis may occur prior to or during an episode of pneumonia. The presence of cough suggests that the pharyngitis is not caused by GABHS. Mycoplasmal pharyngitis might be associated with other constitutional symptoms such as headache and abdominal pain or gastrointestinal symptoms in addition to cough. Infections due

to these organisms are treated with macrolide antibiotics or with tetracycline.^{44,45}

Viral Causes

Cytomegalovirus: Infection with cytomegalovirus presents in a fashion similar to EBV infection but with much milder symptoms. This virus should be considered in the patient with a clinical picture resembling mononucleosis but whose tests for EBV prove negative. Cytomegalovirus can be cultured, and there are specific antibody tests for the virus, but these are generally not indicated.⁴⁴

Adenovirus: Adenovirus often presents as an intense exudative pharyngitis. In about half the cases, the patient also has follicular conjunctivitis, which can be unilateral or, less commonly, bilateral. In patients with so-called "pharyngoconjunctival fever," no further diagnostic evaluation is required. Although a few patients with adenovirus become quite ill, in the vast majority of cases, the patient has about 1 week of uncomplicated pharyngitis followed by the resolution of symptoms.^{44,45}

Herpes Simplex: Although many patients with primary herpes simplex infections complain of sore throat, the disease involves the mouth as well. In most cases the diagnosis is made by the symptoms (which may include blisters on the tongue and lips, increased salivation, halitosis, and painful sores) coupled with the presence of multiple shallow ulcers distributed over the entire oral cavity. Herpes simplex gingivostomatitis and pharyngitis are self-limited in immunocompetent individuals. However, the patient may experience significant pain, resulting in decreased oral intake and dehydration, so attention to pain control and hydration is mandatory. Severely affected patients may require antiviral therapy.^{44,45}

Coxsackievirus: Coxsackievirus also presents with pharyngitis associated with ulcerative lesions. However, the lesions of coxsackievirus are fewer in number, located in the posterior pharynx, and are often larger than those found in herpesvirus infections.^{44,45}

Influenza virus: Pharyngitis is often a part of the clinical picture in patients infected with influenza type A or B.

As is the case for many types of viral pharyngitis, the constellation of associated symptoms will help the ED clinician distinguish influenza from GABHS. The pharyngitis associated with influenza is nonexudative, and the patient does not have cervical adenopathy. Furthermore, most patients experience other symptoms such as cough, myalgias, and headache.⁴⁴

Noninfectious Causes Of Pharyngitis

A variety of noninfectious processes can cause pharyngitis. In general, all these processes result in pharyngeal irritation. Examples include smoke inhalation, thermal or chemical burns, swallowed objects (either foreign substances or foods), and vocal strain. Allergens may result in mild pharyngeal irritation, either directly or as an effect of posterior nasal discharge. Other causes may include thyroiditis or malignancy. Gastroesophageal reflux disease has been proposed as the etiology for chronic episodes of pharyngitis. In recent small studies, treatment of reflux has resulted in a statistically significant decrease in nonspecific pharyngitis.^{x,x1}

In most cases, the diagnosis can be made or at least suspected based on the history alone. In more subtle cases, the ED clinician need only exclude serious causes of pharyngitis in order to refer the patient for further evaluation.⁴⁴ Other systemic disorders such as rheumatologic disorders (eg, Still's disease, named for the English clinician George Frederick Still)^{xii} or endocrine disorders (eg, Sjögren's syndrome) may result in pharyngitis.^{xiii} Finally, some cases of pharyngitis have interesting and unusual causes. In 1 reported case, a patient sustained pharyngeal burns when she inhaled parts of the screen from her disintegrating crack-cocaine pipe.⁴⁸

Prehospital Care

The role of prehospital care providers in the management of the patient with pharyngitis is limited. For the patient who is not toxic, ambulance transport is not required. Emergency medical service personnel should focus on 2 key issues, as described below.

First, they should be alert for signs of respiratory compromise due to upper airway obstruction. When such signs are identified, the patient should receive high-flow oxygen en route to the emergency center. In addition, the patient should be transported in the most comfortable position, which is often a seated or semierect position rather than a recumbent one. Under no circumstances should a patient with signs of upper airway obstruction be forced to recline. Should the patient undergo complete airway obstruction during transportation, he or she should be managed with bag-mask ventilation, tracheal intubation, or a surgical airway. Many so-called "rescue" airway devices, such as the laryngeal mask airway or the Combitube®, may be ineffective in the management of patients with upper airway obstruction. Likewise, the use of transtracheal jet ventilation in cases of complete airway obstruction is, at best, controversial. When faced with a patient whose signs suggest upper airway obstruction, prehospital personnel should consider transport to a facility capable of providing surgical airway management.

Second, many patients with severe pharyngitis

have been unable to maintain adequate hydration. In such cases, the administration of intravenous fluids may make the patient feel better. However, in urban environments with relatively short transport times, intravenous hydration is mandatory only for those patients who are significantly dehydrated. Intravenous access attempts in children with impending airway obstruction may be ill-advised, since emotional upset may worsen the obstruction.

Evaluation In The ED

Initial Assessment

Even though most patients with pharyngitis are not significantly ill and do not require immediate attention, the ED clinician should begin by considering the serious and life-threatening causes of sore throat. Signs of potentially severe disease include dysphonia/aphonia, trismus, drooling, stridor, toxic appearance, and air hunger. In some cases the ED clinician will need to treat the patient's respiratory symptoms before determining their etiology. Before dismissing a case as "just another sore throat," the ED clinician should systematically answer the following questions, and only after these conditions have been ruled out can the ED clinician be reassured that the patient is not seriously ill.

1. Does the patient exhibit signs of existing or impending respiratory compromise?
2. Could the patient have epiglottitis, retropharyngeal abscess, Ludwig's angina, peritonsillar abscess, or infectious mononucleosis with severe tonsillar and lymphoid hypertrophy?
3. Is the patient severely dehydrated?

History

Although few causes of pharyngitis can be identified from the history alone, it can provide clues to the etiology and guide the diagnostic evaluation.

Assuming the patient is not in obvious distress, the ED clinician's first task is to elicit historical clues that would suggest a more serious illness. These include the inability to speak, a muffled voice, severe pain on phonation, or complaints of decreased oral intake due to significant pain. An abrupt onset of symptoms or rapid progression of the illness is of concern, but equally worrisome are symptoms that gradually worsen and do not remit. In such cases, the ED clinician should consider entities such as laryngeal or esophageal tumors and retropharyngeal abscess.^{27,28,44,45}

In more routine cases, the history is important in helping to limit the differential diagnosis. In the most straightforward cases, the patient relates a clear history of inhalational injury, direct trauma, chemical exposure, vocal strain, or other definite causative event. Past exposure to persons with similar symptoms suggests an infectious etiology. As in more seri-

ous cases, the timing of the symptoms is an important consideration. In viral or bacterial pharyngitis, the onset of symptoms is likely to be early in the course of the illness, whereas in infectious mononucleosis a few days of lethargy may have preceded the onset of throat pain.^{30,32,33,44,45} Likewise, associated signs and symptoms are important. For example, GABHS infection is not commonly associated with coryza, cough, conjunctivitis, and viral exanthem, so the presence of several of these symptoms can effectively exclude GABHS from the differential diagnosis.^{41,44,45,49-54} Conversely, a scarlatiniform rash in association with pharyngitis in a school-age child and in the absence of other viral symptoms makes GABHS the most likely cause of the patient's symptoms.^{53,54}

The patient's age, the season, and the geographic location are also important parts of the history. GABHS is far more common in school-age children and in the fall and winter months, whereas infectious mononucleosis is more common in adolescents and young adults.^{30,41,44,45,49,50} The incidence of rheumatic fever and streptococcal carriage varies with geographic location.⁵⁵ Finally, the physician should note any history of recent oral or pharyngeal trauma, dental work, or cosmetic oral piercing.²¹⁻²³ The ED clinician should also inquire about sexual behavior that would suggest possible sexually transmitted diseases such as gonorrhea, HIV infection, and the like.

Past history is equally important. The ED clinician should note a history of rheumatic fever or congenital heart disease, and it is especially important to rule out the possibility of valvular heart disease. Immunization status should be noted, as should a history of immunodeficiency. Patients who have previously had mononucleosis are unlikely to have it again. If the patient reports a medication allergy, it is important to note the type of reaction that occurred. Many patients mistakenly believe that they are allergic to certain medications because they experienced an untoward but nonallergic reaction to a previous dose of medication (eg, vomiting after erythromycin). Prior surgical history is likewise important — ie, a patient who has had a tonsillectomy obviously cannot have tonsillitis.

Finally, the patient should be asked about his or her own attempts to treat the symptoms. Home remedies, herbal treatments, and traditional medicines all can contribute to the clinical picture. Ask specifically about antibiotics, since many patients present after having treated themselves with leftover antibiotics or antibiotics prescribed for a friend or relative. Although the patient may be embarrassed to admit that he or she has taken medication, this history is potentially important and should be obtained whenever possible.

Physical Examination

In most cases the physical examination begins when the ED clinician enters the examination room. By

that time he or she may already be aware of the patient's vital signs and nursing assessment and may have formed an opinion as to the likely cause of the patient's symptoms, as well as the likelihood of serious or life-threatening illness. Tachycardia, tachypnea, and/or hypotension are clearly of concern and should prompt an immediate and thorough evaluation. The presence of fever strongly supports an infectious etiology.

Identification and management of existing or impending airway obstruction takes precedence over other aspects of care, and the ED clinician must be alert for signs of this condition. Severely affected patients will prefer to lean forward with their necks extended. When they attempt to recline, their symptoms worsen. Because they are unable to swallow, drooling is a common sign. Likewise, such individuals may have muffled speech or may be unable to speak at all.¹⁰

In addition, the ED clinician should be alert for signs of dehydration, since some patients experience significant odynophagia and are unable to maintain an adequate fluid intake. In addition to tachycardia, the patient may have sunken eyes, dry or "tacky" mucous membranes, and decreased skin elasticity.

In more routine cases, the examination begins with the initial introductions. The quality of the patient's voice is an important clue to the possible pathology. A muffled voice may suggest a more serious condition. Next, the ED clinician should ask the patient to open his or her mouth and protrude his or her tongue. Trismus indicates severe inflammation and is often associated with peritonsillar abscess or severe peritonsillar cellulitis.^{26,28} Inside the oral cavity, the ED clinician should look for dental disease and ascertain whether the tongue appears to be elevated. Both are clues to Ludwig's angina. This diagnosis is supported by a firm, almost "woody" feeling when the sublingual and submental tissues are palpated.²¹⁻²³ The oral and buccal mucosa should be examined for the presence of lesions. Multiple ulcerations in the anterior mouth suggests primary herpes, while the presence of a few larger lesions on the soft palate is more indicative of coxsackievirus infection.^{44,45}

In the posterior pharynx, attention should be directed to the tonsils (if present) and the uvula. Relatively large but uniform tonsils are normal in young children. However, unilateral enlargement and peritonsillar cellulitis are findings classically associated with peritonsillar abscess and tonsillitis. In addition, the enlarged tonsil may have displaced the uvula laterally. In cooperative older children and adults, a fluctuant mass may be seen or palpated in the palatal tissue surrounding the tonsil.²¹⁻²³ Inflamed tonsils with exudates are typical of many types of infectious pharyngitis. However, diphtheria causes a gray membrane that is adherent to the tonsils and posterior pharynx. Attempted

removal of the membrane reveals a hemorrhagic base. In some cases of infectious mononucleosis, the tonsils become so enlarged that the patient develops symptoms of upper airway obstruction.³⁰ Likewise, several infectious and noninfectious inflammatory conditions can cause significant edema of the uvula; in some cases, the uvula may become so enlarged that it presents the potential for obstruction.⁴⁴

Examination of the palate can also be helpful in identifying the cause of the patient's symptoms. Palatal petechiae in particular are more often associated with bacterial pharyngitis. As mentioned previously, masses or bulging of the pharynx can suggest peritonsillar abscess and are occasionally seen at or near the midline of the posterior pharynx in patients with retropharyngeal abscesses.^{21-23,27,44,45}

Examination of the neck is also important. Limited neck mobility, particularly the inability or unwillingness to extend the neck to look up (Bolte's sign), has been shown to be a reliable sign of retropharyngeal abscess.²⁷ A recent report demonstrated the subtle nature of the presenting symptoms of retropharyngeal abscess in young children. The ED clinician who considers the diagnosis only in those children with signs of upper airway obstruction will not identify many patients. Attempting to distract the child into looking up can help in the identification of less obvious cases. Children with a retropharyngeal abscess will look up only with their eyes, whereas unaffected children will look up by extending their necks.²⁷ The neck examination also includes palpation of the lymph nodes. The finding of enlarged, tender anterior cervical nodes is 1 of the Centor criteria (the others being history of fever, absence of cough, and tonsillar exudate) (see **Rules For Adults** for a more detailed explanation of these criteria), and their presence is an important clue to the diagnosis of GABHS.⁵¹ On the other hand, enlarged posterior cervical lymph nodes are more often associated with infectious mononucleosis.^{30,32,33}

The remainder of the physical examination is also of value. Patients with other symptoms suggestive of viral illness are not likely to have a GABHS infection.^{41,44,45,49-54} These include conjunctivitis, rhinorrhea, viral exanthem, serous otitis media, cough, and wheezing. Unilateral or, less commonly, bilateral follicular conjunctivitis associated with exudative pharyngitis is a hallmark of adenovirus infection.⁴⁴ In a school-age child with pharyngitis, the presence of a scarlatiniform rash, on the other hand, is almost diagnostic, and many ED clinicians advocate treating such patients without testing.^{53,54} Although the agent *Arcanobacterium haemolyticum* produces a very similar rash, patients with *A haemolyticum* infections are generally older and more often have an associated cough. Their rash is highly pruritic and, unlike the rash of scarlet fever, does not peel.^{44,46} Patients with infectious mononucleosis often have splenomegaly, and some have hepatomegaly as well. If treated with

amoxicillin, patients with infectious mononucleosis often develop a morbilliform rash. Such a rash in a patient with the appropriate history should be considered de facto evidence of EBV infection.^{30,32,33}

The spleen is the predominant organ in the left upper quadrant. It is classically difficult to palpate the spleen based on its location immediately beneath the left hemidiaphragm. With the advent of bedside sonographic technology, however, it has become easier to detect splenomegaly. ED clinicians may look for an echogenic structure immediately superior to the left kidney and lateral to the adrenal glands. Although there are few validated criteria for splenomegaly, a good rule of thumb is that in 95% of healthy adults the length of the spleen is less than 12 cm.^{xiv}

Finally, patients infected with coxsackievirus A 16 may have the hand, foot, and mouth syndrome, in which the patient presents with ulcers on the hands, feet, genitals, and/or buttocks, in addition to oral and pharyngeal lesions.^{44,45}

Rules For Clinical Decision-Making

Clinical decision rules or scoring systems are designed to reduce the subjectivity of clinical decision-making by providing the physician with a list of clinical symptoms or signs that either increase or decrease the patient's likelihood of having GABHS. Several rules for both adults and children have been developed.

Cost-Effectiveness Rules

One of the key reasons for the development of clinical decision rules is to provide cost-effective treatment while avoiding unnecessary exposure to antibiotics and complications of either the disease or its treatment.

Among the earliest rules are those developed by Tompkins. The Tompkins rules are based on the costs of various testing and treatment strategies and take into account the costs associated with rheumatic fever and its attendant complications, the costs of the treatment itself, and the costs associated with caring for individuals who have an allergic reaction to penicillin. (The rules do not account for the costs associated with missed work, alternative daycare arrangements, and other "social costs.") The rules are older and do not consider the costs of alternative antibiotics or RADTs. The Tompkins rules recommend that all patients with at least a 20% chance of having a GABHS infection be treated presumptively without obtaining a culture. Conversely, those with less than a 5% chance would undergo neither culture nor treatment. Those patients with a 5% to 19% chance of having a GABHS infection should have cultures performed.⁵⁶

Tsevat et al performed a similar analysis. They compared the cost-effectiveness of 7 strategies, which included neither testing nor treating anyone, treating all patients presumptively without testing,

and various combinations of testing and treating, including the use of RADTs. They concluded that in a population of what they termed “adherent” patients, the most cost-effective strategy was throat culture followed by treatment only for those patients whose culture results were positive.³⁸

The Tsevat study, while interesting, is more applicable to office-based practitioners with a reliable patient base. The Tompkins rules can be used to justify presumptive therapy but, given the low risk of rheumatic fever, would result in gross overtreatment if rigorously followed.

Rather than slavishly applying these criteria, ED clinicians should simply understand that there is a real or potential cost, whether immediate or delayed, associated with any treatment strategy. Presumptive treatment should be administered to patients with a reasonable chance of having a true infection, whereas those with a very low chance should be treated symptomatically. Patients with an intermediate risk are the best candidates for testing.

Rules For Adults

Perhaps the best known clinical decision rules for pharyngitis are those published by Centor et al in 1981.⁵¹ They used logistic regression models to create a 4-item score. The 4 items were: (1) tonsillar exudates; (2) swollen, tender, anterior cervical lymph nodes; (3) lack of a cough; and (4) a history of fever. In a group of 286 patients over 15 years of age, they found that patients who met all 4 criteria had a 56% probability of having a positive culture, whereas those who met none of the criteria had only a 2.5% probability of having a positive culture.⁵¹ These rules have been prospectively validated in 3 adult populations and are considered to be highly reliable.^{51,57,58}

McIsaac et al modified the Centor criteria slightly by adding 2 age-based criteria. In the McIsaac modification, 1 additional point is added if the patient is under 15 years of age, and a point is subtracted if the patient is 45 years of age or older. Patients with a McIsaac score of 0 or -1 have a 1% chance of having a positive throat culture, whereas those with a score of 4 or 5 have a 51% chance of having a positive throat culture.⁵⁷

Walsh et al created a branching algorithm based on criteria similar to those used by Centor but also including a history of exposure to GABHS. Using the algorithm in a group of 418 adults, patients were sorted into high-, moderate-, and low-risk groups. Those patients in the high-risk group had a 23% to 28% chance of having a positive throat culture, those in the moderate-risk group had a 12% to 15% chance, and those in the low-risk group had a 3% to 4% chance.⁵²

There have been some criticisms of the Centor rules. In a study published in 2004, the investigators at a family medicine clinic performed throat cultures and RADT on 787 children and adults, ages 3 to 69,

who presented with acute sore throat. Recommendations from the IDSA and the American College of Physicians–American Society of Internal Medicine (ACP–ASIM) were compared with results on RADT, a clinical prediction rule (the Modified Centor rules), and a criterion standard of treatment for positive throat culture results only. The conclusion for the study suggests that empirical treatment of adults having a Centor score of 3 or 4 is associated with a high rate of unnecessary antibiotic use.^{xv} It is for this reason that the IDSA has not come out in full support of the Centor rules.

Nevertheless, the Centor rules are well-validated and have been endorsed by several respected specialty societies and the CDC.⁶ It is highly unlikely that patients with a Centor score of 0 have GABHS and, given the somewhat lower risk of complications in adult patients, they can be treated symptomatically. Those with scores of 4 can be treated presumptively or tested (with RADT), at the discretion of the ED clinician, with the understanding that they have a 56% chance of having a positive throat culture. Depending on the circumstances, patients with scores of 2 or 3 can be tested, and only those with positive tests would be treated. Or, one can simply treat all patients with scores of 3 or 4 with antibiotics and give those with scores of 2 or less symptomatic treatment only.⁶

Robert Maccabee Centor, in a recently published editorial, also gives further reasoning for the continued use of his scoring criteria.^{xvi} He notes that randomized trial data suggest a significant decrease in symptoms (2.5 days in adults with GABHS and 1 day in those with non-GABHS symptoms). Another reason to err on the side of (judiciously) prescribing antibiotics was to decrease the rate of epidemic pharyngitis. Until more definitive data are available, the ACP–ASIM Protocol utilizing Centor rules continues to be widely accepted as the standard of care.

The McIsaac modification of the Centor rules should be valid as well, but they have not been as rigorously tested as the original rules. The Walsh branching algorithm is not as effective as the Centor rules.^{52,57}

Rules For Children

In 1977 Breese developed what he called a “simple scorecard” for the diagnosis of GABHS. This was a 9-item, weighted scoring system with a maximum possible score of 36 points. Unfortunately, the scoring system recommends the routine use of a white blood cell count. In addition, the validation study contained significant methodologic flaws. These problems make this system impractical for routine use.⁴⁹

In 1998 Wald et al published a study of a simplified version of the Breese scorecard.⁵⁰ They eliminated the white blood cell count and instead evaluated 6 items: (1) age; (2) season; (3) temperature of at least 38.3°C (100.9°F); (4) adenopathy; (5) pharyngeal

erythema, edema, or exudates; and (6) no symptoms of viral upper respiratory tract infection. The maximum possible score was 6. In a group of 365 children they found that a score of 5 or 6 predicted a positive culture in 59% and 75% of patients, respectively. On the other hand, a significant number of children with scores of 2 or 3 had positive throat cultures.⁵⁰

Attia et al developed and tested a 4-item model. The items in their model included tonsillar swelling, cervical lymphadenopathy, and absence of coryza (valued at 1 point each) and presence of a scarlatini-form rash (valued at 2 points) for a total possible score of 5 points. A patient with a score of 0 had only a 12% chance of having a positive throat culture (approximately the GABHS carriage rate in the community studied), whereas a patient with a score of 4 or more had a 79% chance of having a positive throat culture. Unfortunately, a score of 4 or 5 points was only possible in the presence of a scarlatiniform rash, a relatively rare finding. Those patients with a score of 1 to 3 had, in aggregate, only a 36% chance of having a positive culture.^{53,54}

Mclsaac et al developed a modification of the Centor rules (as discussed in the section **Rules For Adults**). In their validation study of 167 children and 453 adults, a patient with a score of 4 or 5 had a 51% chance of having strep throat.⁵⁷

The results of these studies suggest that children with a score of 5 or 6 using the Wald scorecard, a Mclsaac score of 4 or 5, or those with a scarlatini-form rash associated with other typical symptoms of GABHS infection can be treated presumptively. Unfortunately, none of these methods can be used to exclude GABHS without testing.

At this time, the ASIM, the American Academy of Pediatrics (AAP), and the IDSA are in agreement in obtaining the RADT on all children, treating those who have positive test results, and obtaining a throat culture from those who have a negative result.^{xvii}

Diagnostic Testing

Laboratory Tests

Throat Culture

When clinical decision rules and rapid detection tests are discussed, their sensitivity and specificity are virtually always compared to the “gold standard” of the throat culture, which is 90% to 99% sensitive for the detection of GABHS infection. It is, of course, nearly 100% specific for the presence of the bacteria in the pharynx; however, this may reflect a carrier state and not disease. The distinction between these states requires antibody testing.^{41,44,45} Conversely, patients with relatively small numbers of organisms in their throats (eg, carriers) may not have positive throat cultures.⁴⁴

Another drawback is that the results depend heavily on the technique used to obtain the sample.

The physician or nurse who attempts to obtain a culture from a crying and uncooperative child by shoving a swab somewhere into the child’s mouth is wasting money and time. Instead, the swab should be passed along the surface of the tonsils (in patients who have undergone tonsillectomy, the tonsillar fossa is an acceptable alternative) and the posterior pharynx.⁵⁹ Using 2 swabs improves the odds of obtaining a positive culture.

From the perspective of the ED clinician, however, the primary problem with the throat culture is the time delay in obtaining results. This delay is problematic for several reasons. The ED must establish a method for contacting those patients with positive cultures and arranging for them to be treated. Records must be kept so that attempts at contact are verifiable. Such systems can become time- and labor-intensive. The patient may be forced to miss 1 or more days of school or work while waiting for the test result and is often further inconvenienced by a second medical visit. Finally, 1 of the benefits (albeit relatively minor) of treatment prior to receiving the test result is that the patient’s symptoms might improve 24 to 48 hours sooner. A delay in treatment while awaiting culture results is likely to preclude this benefit.⁴⁴

If the patient history suggests the possibility of gonococcal pharyngitis, routine throat culture on sheep’s red blood cell agar is not the test of choice. Suspected infections should instead be confirmed by culture on Thayer-Martin agar.^{45,47} Because certain nonpathogenic strains of *Neisseria* colonize the pharynx (especially in young children), and because of the potential consequences of the diagnosis of gonococcal pharyngitis, obtaining a second set of confirmatory cultures is recommended. Newer DNA probe tests for *N gonorrhoeae* are not recommended for the diagnosis of gonococcal pharyngitis.^{47,60}

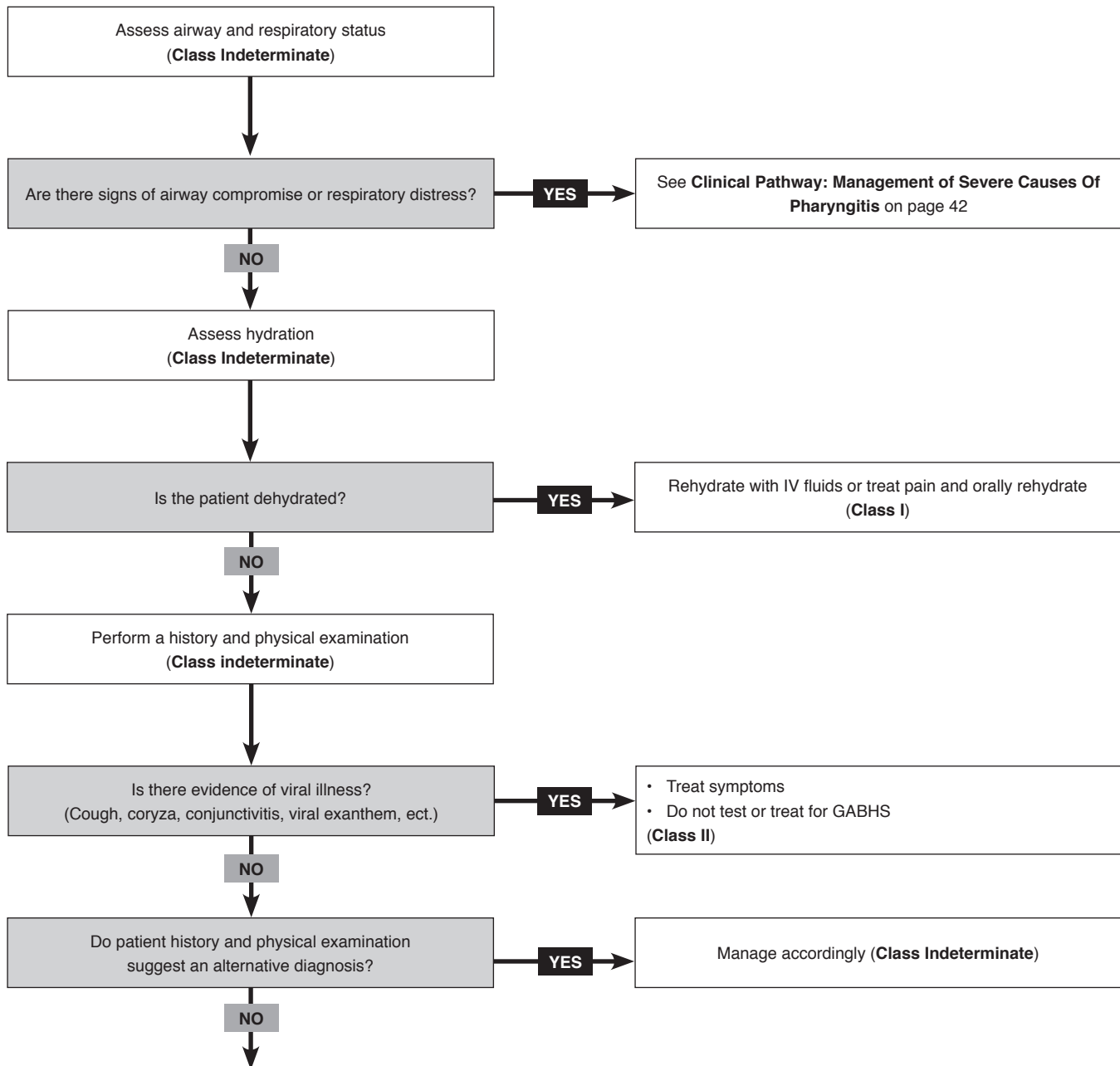
Rapid Antigen Detection Tests

RADTs became available in the 1980s and have rapidly evolved. RADT testing is done in a fashion similar to the throat culture. A swab is passed over the tonsils and the posterior pharynx. In a person with pharyngitis, the presence of GABHS provides the source of bacterial antigens for the test. This material is treated and then exposed to antibodies against GABHS. A marker is used to detect the antigen-antibody complex. Early systems were based on latex agglutination technology. Because this test involves several steps and requires subjective interpretation by a technician, there are many opportunities for the technique to fail. It should come as no surprise that these tests have relatively low sensitivities (mean, 80%; range, 62%–97%).^{61,62}

The next RADT tests to be developed and released were based on the enzyme-linked immunosorbent assay (ELISA). ELISA technology still

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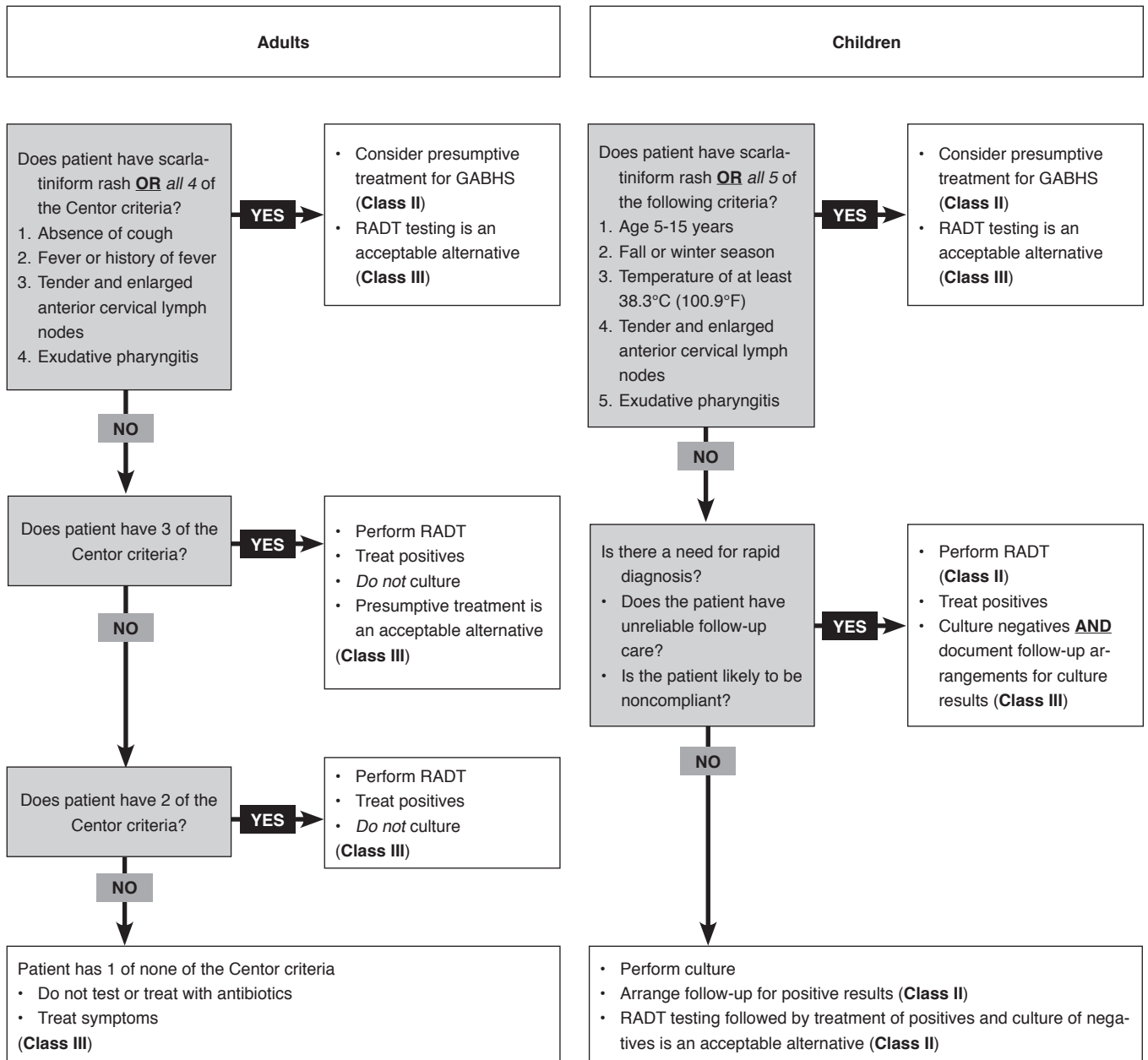


Go to "Adults" or "Children" portion of pathway on next page

For Class Of Evidence Definitions, see page 1.

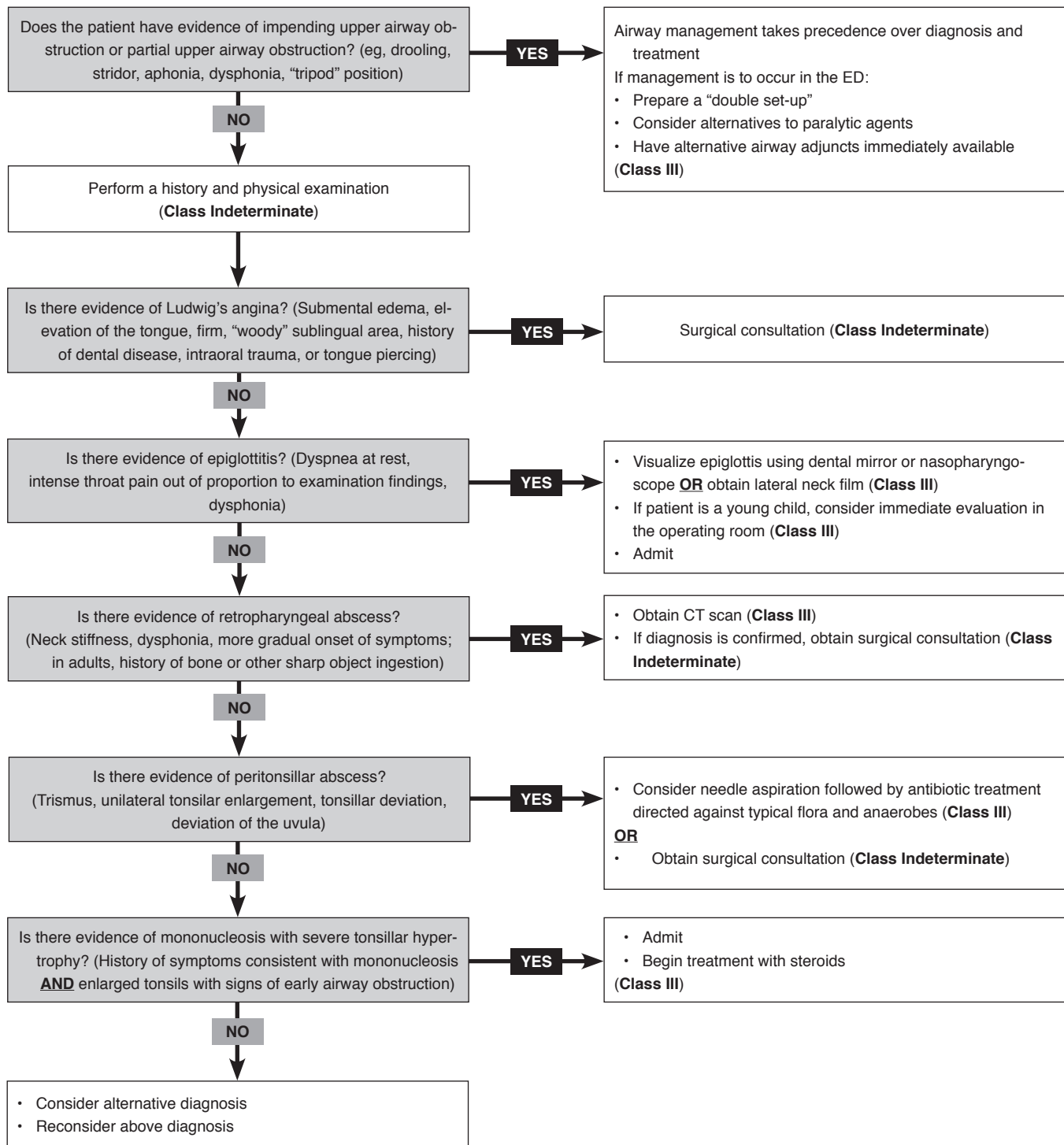
Clinical Pathway For Evaluation And Management Of Pharyngitis

(continued from page 40)



For Class Of Evidence Definitions, see page 1.

Clinical Pathway For Management Of Severe Causes Of Pharyngitis



For Class Of Evidence Definitions, see page 1.

involves several steps; however, the use of a color indicator means that the result is less reliant on subjective interpretation by laboratory personnel. Unfortunately, the ELISA tests have a performance profile very similar to that of latex agglutination (mean sensitivity, 79%; range, 61%–96%).^{61,62}

The current generation of tests (initiated more than a decade ago in 1994), primarily employs optical immunoassay (OIA) technology. OIA tests rely on the changes in the reflection of light to indicate that the antibody has bound to the antigen sample. Test results are generally available in less than 1 hour, allowing a treatment decision to be made while the patient is still in the ED. Many studies comparing OIA detection test to GABHS culture have been conducted. Virtually all agree that OIA detection tests are very specific for GABHS. In light of a positive test, the patient can be assumed to have streptococcal pharyngitis and can be treated accordingly.

More recent RADTs manufactured by several different companies that have improved this technology have enabled ED clinicians to obtain results in less than 15 minutes, thus improving emergency department flow and patient satisfaction and decreasing the need for follow-up. Many of these tests may be conducted solely by the ED clinicians themselves. A comparison of these newer RADTs (using technology as varied as latex agglutination, enzyme immunoassay, optical immunoassay, chemiluminescent DNA probes, and PCR methods) demonstrated comparable results, with sensitivities greater than 90% and specificities greater than 95% in the detection of GABHS pharyngitis.^{xvii} This echoed the findings of the high specificity of the previous generation of RADT tests. However, given the lower sensitivity of these tests, a throat culture should still be obtained if results are initially negative for GABHS.

RADTs also have the same potential failings that cultures do. Like cultures, they rely on a properly collected specimen — and, like cultures, the technique used to perform the test can influence the results. Some have noted that in many cases in which the RADT result is negative but the culture is positive, the culture has a very low bacterial colony count. This has led to the postulation that these are patients with very few organisms in their throats (perhaps GABHS carriers with nonstreptococcal pharyngitis).

There is another potential problem with RADTs. A recent study demonstrated that these tests are subject to so-called spectrum bias. That is, the sensitivity of the test varies with the likelihood of disease in the subject. In this study, the RADT was 61% sensitive in subjects with none or 1 of the Centor criteria, 76% sensitive in those with 2 Centor criteria, 90% sensitive in those with 3 Centor criteria, and 97% sensitive in those with 4 Centor criteria. These findings

imply that, among other things, in patients who meet 3 or 4 Centor criteria but have a negative result on RADT, confirmatory cultures may be unnecessary and may serve to explain the wide variation in the reported sensitivities of these tests.⁶⁶

For all of these failings, RADTs perform as well as or better than most clinical decision rules, although they are more costly.

Antistreptolysin O Testing

The human host produces antibodies to certain components of the GABHS cell wall (somatic or cellular antigens) and to substances produced by the organism (extracellular antigens). The test for antistreptolysin O (ASO), the antibody directed against an antigenic hemolysin produced by the GABHS organism, is most familiar to ED clinicians. It has been used for many years to track the recovery of patients with rheumatic fever and poststreptococcal glomerulonephritis. In recent years, ASO titers and other antibody tests have been incorporated into commercial kits, making these measurements easier to obtain.

However, as a clinical tool, antibody tests have many drawbacks. The most important problem is that 1 single titer says little about the status of the patient's condition. There is no reference standard for a "normal" ASO titer. Many factors affect the immune response to GABHS infection, including the age of the patient, the underlying incidence of the disease in the population, the site of the infection (eg, pharyngitis produces a more vigorous antibody response than skin infection), the season of the year, and whether or not antibiotics were given and the timing of such treatment. Antibody testing, therefore, is only useful in tracking the course of an illness in an individual patient. The initial titer is only useful in the presence of later "convalescent" titers. This limitation makes antibody testing nearly useless to the ED clinician.⁶⁷

Heterophile Antibody Testing For Mononucleosis

EBV infection can be identified with certainty by a variety of antigen tests; however, most are expensive and labor-intensive. The most commonly used surrogate for specific tests is the heterophile antibody response (Monospot). This test is inexpensive and readily available but imperfect — it is not specific for EBV. Furthermore, since the antibody response requires some time, the test may not be positive early in the course of illness. Only 60% to 70% of patients have a positive heterophile antibody test result during the first week of illness. By the third week, 80% to 90% of patients will have a positive result. In 15% to 20% of adolescent and young adult patients with a true infection, the test remains negative. In young children, even fewer have a positive heterophile antibody test.³⁰

Complete Blood Count

In the evaluation of the patient with pharyngitis, the role of the complete blood count (CBC) is limited and should not be routine. Although patients with either bacterial pharyngitis or an abscess are likely to have an elevated white blood cell count, in most cases the CBC is of no assistance in making a diagnosis and is not mandatory. Patients with infectious mononucleosis do often have atypical lymphocytes noted on peripheral smear. This finding may help the ED clinician to confirm his or her suspicions, particularly when the ED clinician is evaluating the patient early in the course of illness, when the heterophile antibody test result is most likely to be negative.³⁰

Radiologic Tests

Soft Tissue Lateral Neck Film

The soft tissue lateral neck film is used primarily in the evaluation of patients with symptoms of upper airway obstruction. A properly performed soft tissue lateral neck film can help the physician diagnose epiglottitis, retropharyngeal abscess, and pharyngeal, esophageal, or tracheal foreign bodies, and, when combined with an AP soft tissue neck film, croup. For patients with epiglottitis, the classic finding is enlargement of the epiglottis (also known as the "thumbprint sign"). It is important to understand that inflammation of the epiglottis is not an isolated occurrence. Other tissues near the epiglottis are also inflamed, and their appearance on x-ray will be altered. The entire area around the epiglottis appears edematous. Furthermore, the lateral neck film may be less helpful in the diagnosis of adult epiglottitis than in pediatric epiglottitis.^{10,17} When the symptoms are strongly suggestive, direct examination of the epiglottis is preferred for adults.^{10,16,17}

For patients with retropharyngeal abscess, the classic finding on soft tissue lateral neck film is widening of the retropharyngeal soft tissues. This begs the question, "How wide is too wide?" There is no single answer to this question. Over the years, various rules of thumb have been suggested. The most common of these states that the prevertebral space anterior to the second cervical (C2) vertebra should be no larger than the width of the vertebral body itself, provided that the patient is a young child.⁶⁸ More precisely stated, the retropharyngeal tissues should be 7 mm or less as measured from the most anterior portion of C2. The retrotracheal space should be measured from the anterior aspect of C5 or C6 and should be less than 14 mm.^{29,68} No evidence has demonstrated this rule to be superior to the clinician simply looking at the film and using his or her judgment. In order to provide the most useful information, the patient must be properly positioned. The retropharyngeal space will appear falsely enlarged unless the patient's neck is well extended and the film is taken on full inspiration.²⁹ When the patient is a

young child (the typical victims of retropharyngeal abscess are young children), a useful radiograph may be difficult to achieve. Furthermore, CT scanning has been demonstrated to be more sensitive than plain radiographs and should therefore be considered the modality of choice when retropharyngeal abscess is strongly suspected.^{27,29,68,69}

Most radiopaque foreign bodies are readily detectable on plain radiographs. However, only a few foreign bodies are radiopaque. In practice, plain films are most useful in the identification of metallic foreign bodies (eg, coins). This modality is less useful for objects that are less dense.⁷⁰⁻⁷² While the appearance of these objects on plain x-ray is often touted as a means by which to distinguish between tracheal and esophageal foreign bodies, in practice, objects located within the trachea cause more serious respiratory symptoms. Furthermore, many objects that will readily pass into the esophagus are too large to enter the trachea.⁷³

Although laryngotracheobronchitis, commonly called "croup," is largely a clinical diagnosis, when doubt exists or when other diagnoses are being considered, AP and soft tissue lateral neck films may be useful. On the AP view, the classic finding in croup is narrowing of the tracheal air column in the subglottic region (also known as the "steeple" sign); on the lateral film, a "foggy" or "ground-glass" appearance is commonly noted in the subglottic area.⁷⁴

Computed Tomography

CT is the modality of choice in the evaluation of suspected abscesses. When the clinician strongly suspects that the patient has, for example, a retropharyngeal abscess, many experts argue that plain x-rays are superfluous and should be omitted in favor of a CT scan.^{27,29,68,69} CT is also useful in the evaluation of patients with Ludwig's angina.²¹⁻²³

For all of its advantages, however, CT scanning does have some drawbacks. The patient must lie supine, if only for a few minutes, and this may be difficult or impossible when the patient has symptoms of airway obstruction. Likewise, young children, unless sedated, may move during the study. Movement can be reduced or eliminated with sedation, but this has attendant risks. Finally, CT scanning exposes the patient to significantly more radiation than does plain radiography.⁷⁵

Treatment

Airway Management

Although a complete discussion of emergency airway management is beyond the scope of this article, it is the first priority for the patient with respiratory distress. The patient with complete airway obstruction obviously requires immediate management. It is appropriate to attempt bag-valve-mask ventilation

(the 2-person technique is recommended and often required to achieve adequate ventilation) as the initial management technique. If adequate ventilation with the bag-valve-mask cannot be achieved, and orotracheal intubation cannot be accomplished, it will be necessary to create a surgical airway.⁷⁶

For patients with impending airway obstruction, administration of 100% oxygen is the first priority. Definitive management of the airway might occur in the ED, the intensive care unit, or the operating room, depending on local protocols and the availability of personnel and equipment. If the underlying cause of the patient's symptoms might require surgery, the appropriate surgeon should be notified as soon as possible.

Peritonsillar Abscess

In the past, most patients with a peritonsillar abscess were admitted to the hospital and underwent incision and drainage followed by antibiotic treatment. Recent evidence, however, suggests that needle aspiration may be just as effective, although it may be associated with a higher rate of recurrence. Experienced ED clinicians may undertake this procedure but must take care to avoid complications, the most serious of which is inadvertent puncture of the carotid artery.^{77,78} In addition to having the abscess aspirated, most patients should be placed on antibiotics. Currently, clindamycin and second- or third-generation cephalosporins are the recommended agents.²⁵ With proper aspiration, antibiotic treatment, and appropriate follow-up, many patients with peritonsillar abscesses can be managed as outpatients.^{25,77,78}

Infectious Mononucleosis With Impending Airway Obstruction

Although most cases of infectious mononucleosis are little more than an annoyance, a few patients will develop significant lymphoid hypertrophy. A subset of these patients (0.1%–1.0%) will go on to develop signs of airway obstruction. In these patients, treatment with corticosteroids is generally recommended to reduce the tonsillar hypertrophy and thus to reduce the obstructive symptoms.⁷⁹ Unless the patient has difficulty swallowing, prednisone (1 mg/kg/day; maximum dose, 60 mg) is generally effective. Intravenous methylprednisolone (2 mg/kg/day; maximum dose, 125 mg) is an acceptable alternative.

Infectious Pharyngitis

Treatment of infectious pharyngitis consists of therapy to reduce patient discomfort and antibiotic treatment aimed at the infectious agent when appropriate. However, there is often little in the way of medical evidence to support many of these therapies. For example, an antihistamine, with or without a decongestant, could theoretically eliminate the

posterior nasal drainage that causes pharyngeal irritation associated with viral upper respiratory tract infection; however, most studies of these agents find that they provide little or no benefit.⁸⁰

What most patients desire is relief from the sore throat. Such treatments come in a variety of forms. Some are over-the-counter medications, available at virtually any pharmacy or supermarket, while others require a prescription.

First, and easiest to use, are nonprescription analgesic medications to reduce fever and help alleviate body aches. These include acetaminophen, aspirin, ibuprofen, and naproxen. Each of these agents has advantages and disadvantages. In appropriate doses, all are relatively effective pain medications, and most are available in inexpensive generic preparations. One study of children with pharyngitis compared the effectiveness of acetaminophen, ibuprofen, and placebo and found that by 48 hours, pain had resolved in 80% of ibuprofen-treated children, 70.5% of acetaminophen-treated children, and 55% of those who took the placebo. The difference between ibuprofen and placebo was statistically significant, whereas the differences between acetaminophen and placebo and between acetaminophen and ibuprofen were not.⁸¹

If the patient has significant pain that has not been relieved by 1 of these agents, the physician can certainly consider treatment with an oral narcotic agent. Of the 3 commonly prescribed oral narcotics — codeine, oxycodone, and hydrocodone — the latter 2 are slightly more effective and are associated with fewer unpleasant side effects.⁸²

A variety of topical agents are also available. Topical sprays containing benzocaine and/or phenol are available over the counter and in prescription preparations. These sprays provide temporary relief from pain and might allow the patient to ingest enough liquid to maintain adequate hydration or to swallow analgesic capsules or tablets without undue discomfort. On the other hand, they affect the taste buds and are rapidly washed away by saliva and consumed liquids.

These analgesic medications are very safe if used in the recommended doses. However, there is little or no evidence to support their use. German investigators compared the effectiveness of lozenges made from the mucolytic ambroxol hydrochloride to placebo lozenges and found that ambroxol hydrochloride provided superior pain reduction.^{83,84} Unfortunately, this agent is not available in the United States. Likewise, British and Australian investigators have demonstrated that lozenges containing 8 mg of flurbiprofen are superior to placebo in reducing the pain associated with sore throat. Currently, flurbiprofen is only available in the United States as an ocular preparation.⁸⁵

Finally, no discussion of symptomatic treatment

1. **“How could it have been epiglottitis? This guy was 45 years old. Besides, his throat didn’t look bad at all!”**

Cases of epiglottitis have been occurring more frequently in the last few years. Adults with epiglottitis often present in subtle fashion, complaining of intense throat pain and hoarseness. Dyspnea upon presentation is a very worrisome sign. The ED clinician should be especially wary of the patient with significant throat pain with a relatively benign-appearing posterior pharynx. A simple lateral neck x-ray is often diagnostic. It is also perfectly acceptable to attempt to visualize the epiglottis with a dental mirror or a nasopharyngoscope.

2. **“Sure, the kid was in distress—but with epiglottitis out of the picture, I figured it would be okay just to sedate him and take a look in the ED.”**

Pediatric epiglottitis is but 1 form of upper airway obstruction, and *Haemophilus influenzae type B* is not the only cause of epiglottitis. Chemical and thermal injury and, uncommonly, other types of infection can result in edema of the epiglottis and its surrounding tissues. Management of any patient with impending airway obstruction is best conducted in the most controlled environment possible. Definitive management in the ED should be considered as a last resort. When forced to manage a patient with airway obstruction in the ED, the ED clinician should have several alternative airway devices available and, in most cases, should prepare for a surgical airway with a “double set-up.”

3. **“Hey, it was just a sore throat. What do you mean, she came back the next day severely dehydrated?”**

Pharyngitis can be exceptionally painful, which makes it difficult for patients to consume enough liquids. The ED clinician should first ensure that the patient is adequately hydrated at the time of his or her initial evaluation and then be certain to suggest or prescribe medications and other strategies to reduce the patient’s pain so that he or she can maintain adequate fluid intake.

4. **“My strategy is a quick exam and a prescription. What’s wrong with that?”**

While many ED clinicians employ a strategy of

presumptive treatment for all cases of pharyngitis, this approach is flawed on several levels. First, many patients would prefer to understand their disease and why the ED clinician is recommending 1 course of treatment rather than another. Second, unnecessary antibiotic treatment increases the cost of healthcare, increases the incidence of resistant bacteria, places the patient at risk for medication allergy and other untoward reactions, and creates an expectation of antibiotics for future illnesses.

5. **“That teenager had all 4 Centor criteria, so I treated her with amoxicillin. Her mom was really mad about the rash.”**

Patients who have infectious mononucleosis can resemble those with GABHS pharyngitis. Penicillin treatment has no impact on the disease, but patients with mononucleosis who take amoxicillin can get a diffuse morbilliform rash. The rash is harmless and doesn’t represent medication allergy; however, many patients find the rash upsetting. The rash can be avoided by treating those in the classic mononucleosis age group with penicillin instead of amoxicillin or by performing a high-sensitivity RADT and treating only those patients with a positive result. Patients who are presumptively treated with amoxicillin should be warned about this possible complication.

6. **“Hey, I work in an ED—I don’t have much use for a social history.”**

In most cases, pharyngitis is a benign, self-limited illness. However, in certain circumstances, more liberal treatment is indicated. It is particularly important to know which patients are at greater risk for more serious forms of pharyngitis and for complications. For example, recent immigrants from certain countries (eg, the former Soviet Union) might be more likely to have diphtheria. Likewise, rheumatic fever, while rare, occurs with greater frequency in certain parts of the United States and in certain countries. (In the United States, outbreaks have been reported in Pennsylvania, Utah, West Virginia, and Texas, among others. Worldwide, rheumatic fever remains a problem in much of the third world.) Patients who are at greater risk for these illnesses are candidates for a thorough evaluation. It is very important to recognize that

virtually all clinical decision rules and treatment pathways designed for pharyngitis were intended for use under normal circumstances. These rules should not be used during outbreaks and should not be applied to individuals at greater risk for serious disease.

7. **“I sent the new tech in to do the rapid strep test. It was negative, but now the throat culture is positive, and I have to call the child back.”**

There are many reasons that the RADT might be negative even though the patient has GABHS pharyngitis. The most common reason is undoubtedly poor collection technique. The swab should be passed over both tonsils and the posterior pharynx. In patients whose tonsils have been removed, the tonsillar fossae are an adequate substitute. Failure to perform the tests correctly can result in false-negative results. All members of the staff responsible for performing these tests should be thoroughly trained in the proper collection method.

8. **“I was worried about a retropharyngeal abscess. The lateral neck film seemed to confirm my suspicions, so I ordered a CT scan. For the patient’s sake, I’m happy that the scan was normal, but I just don’t understand how this could have happened.”**

The soft-tissue lateral neck x-ray remains the screening test of choice for retropharyngeal abscess, although some authors advocate direct CT scanning of high-risk cases. Enlargement of the prevertebral soft tissues suggests the presence of this disease. However, care must be taken to distinguish a truly enlarged prevertebral space from one that only appears to be enlarged. The most common reason for a falsely positive soft-tissue lateral neck film is inappropriate flexion of the patient’s neck. Retropharyngeal abscess is most common in young children, and it can be very difficult for the radiology technician to properly position these often uncooperative patients. Nonetheless, the ED clinician should not accept the film unless the patient’s neck is well extended. Similarly, if the child is crying vigorously at the time the film is taken, the technician should attempt to obtain the x-ray while the patient is in inspiration. Expiratory films of crying children often appear to have large prevertebral spaces.

9. **“I don’t understand it. I wrote a prescription and spent time explaining things to the family. How could the patient have relapsed?”**

There are several possible explanations for treatment failure or relapse in a patient with GABHS pharyngitis. Nonadherence is probably the most common reason. If oral medication is used, most authorities recommend a full 10 days of treatment. Patients who fail to adhere to this regimen are more likely to fail treatment. Some authors have suggested that the presence of other beta-lactamase-producing bacteria in the patient’s throat might prevent beta-lactam antibiotics, like penicillin, from eradicating a sufficient number of GABHS organisms. Patients who fail therapy or relapse shortly after treatment might benefit from treatment with antibiotics effective against beta-lactamase-producing organisms. Penicillin remains the drug of choice for initial treatment in non-allergic patients. Finally, penicillin-allergic patients who are treated with erythromycin might have an infection caused by a strain of GABHS that is resistant to erythromycin. In such cases, treatment with a different agent is warranted.

10. **“I treated the guy with an appropriate antibiotic, but he complained because I didn’t address his need for pain medication.”**

Since only a minority of patients with pharyngitis can be expected to benefit from antibiotic treatment, 1 of the ED clinician’s primary duties is to assess and treat the patient’s discomfort. Some patients will benefit from simple over-the-counter analgesics, gargles, and topical agents, while others might require narcotic pain medications in order to receive maximum benefit. There is a growing body of evidence suggesting that steroid treatment might be beneficial in the subset of patients with documented bacterial pharyngitis. The issue of pain control has long been an important one, but recently it has been the focus of several regulatory bodies. As such, ED clinicians should ensure that all patients with painful conditions receive adequate analgesia.

would be complete without consideration of the role of corticosteroids. Although many practitioners routinely prescribe or administer corticosteroids to patients with pharyngitis, there are no large trials to support this practice. However, the results of a number of smaller studies suggest that corticosteroid treatment provides pain relief several hours sooner than might otherwise be expected.⁸⁶⁻⁸⁹ Early studies centered on the use of intramuscular steroids, but the results of more recent trials indicate that oral agents are equally effective.^{87,88} A single 10-mg dose of dexamethasone (either taken orally or injected intramuscularly) and a single 60-mg dose of prednisone have been demonstrated to be effective in adults. Children should receive a single dose of oral dexamethasone (0.6 mg/kg; maximum dose, 10 mg). Interestingly, the greatest benefits seem to occur in patients who have culture-proven bacterial pharyngitis. Therefore, steroids should be strongly considered in those patients who seem more likely to have bacterial pharyngitis based on the criteria previously discussed. It should be noted that all patients in these studies were also treated with antibiotics and that the use of other analgesic agents was not controlled. It is therefore not possible to determine the effect of steroid treatment as monotherapy for the discomfort of nonbacterial pharyngitis. However, based on these limited studies, corticosteroids do appear to be safe. None of the authors report any significant untoward events associated with the use of corticosteroids.

Antibiotic Treatment Of GABHS

There is little question that despite years of use, penicillin remains remarkably effective in the treatment of GABHS infections. A study that compared GABHS cultures obtained in the 1930s to modern cultures demonstrated that, at least in vitro, penicillin remains a potent weapon.⁹⁰ That being said, some authors have noted both bacteriologic and clinical failures in association with penicillin treatment. Depending on the measure used, roughly 20% to 30% of patients might be expected to “fail” treatment with penicillin or to relapse.^{91,92} While the significance of these failures in terms of placing the patient at risk for rheumatic fever is debatable, no discussion of treatment is complete without addressing these issues.⁹⁰ GABHS bacteria are not the only inhabitants of the human respiratory tract. *H influenzae*, *Moraxella catarrhalis*, and other bacteria are also often present. Many of these bacteria produce beta-lactamase and are therefore resistant to penicillin. Studies comparing patients with significant numbers of beta-lactamase producers in their throats with those who do not harbor such organisms have concluded that penicillin is less likely to eradicate GABHS in the former group. It has been theorized that the beta-lactamase produced by other bacteria actually decreases the concentration of penicillin

in the pharynx, thereby diminishing its effectiveness.^{93,94} Others have found that alpha-hemolytic streptococci play an important role as well. It has been proposed that the alpha-hemolytic bacteria compete with other organisms for nutrients. Patients with lower colony counts of alpha-hemolytic organisms coupled with higher counts of beta-lactamase producers seem to fail treatment with penicillin more often.⁹⁴ These findings have led some to assert that agents more effective against beta-lactamase organisms should either replace penicillin altogether or should be used to treat those patients who have experienced a penicillin failure.^{90,93,95}

Critics of this approach argue that in areas with an overall low incidence of rheumatic fever, the benefits of microbiologic cure are questionable and may not be worth the risks of increasing bacterial resistance and the costs of these agents.^{91,96} Given the difficulties associated with the performance of a definitive study, most ED clinicians will be forced to rely on the recommendations of experts and specialty societies along with their own interpretation of the medical literature.

Treatment of pharyngitis — even documented GABHS pharyngitis — is not without risk. Patients can experience allergic reactions and unpleasant side effects from antibiotic treatment. In addition, some authors have noted higher relapse and recurrence rates among patients treated early in the course of their illness as compared with those who are treated later. These investigators have suggested that later treatment might allow the patient to mount a more vigorous immune response, which may later serve to protect him or her from relapse.⁹⁷ However, other studies refute these findings.⁹⁸ Others have noted that patients who receive antibiotics for 1 instance of pharyngitis tend to seek care for similar symptoms in the future and are more likely to believe that antibiotics are beneficial or necessary.^{98,100}

Although many antibiotics can effectively eradicate GABHS, **Table 2** and **Table 3** list the most commonly recommended agents and their doses for adults and children. **Table 4** (see page 50) lists alternative agents and their doses, and **Table 5** (see page 50) lists agents that are ineffective against GABHS. Other than issues of allergies and other untoward side effects, the choice of treatment method and agent is largely a matter of ED clinician and patient preference. However, the relative costs of the agents used should also be considered.

In many cases, the ED clinician will be restricted to the drugs on a prescription plan formulary. The first question to be answered is, “shot or pills?” An intramuscular injection is very uncomfortable but provides a one-time, single-dose treatment. Parents are spared the need to administer further doses of medication to an uncooperative child, and busy working adults do not have to remember to take antibiotics. No notes allowing medication to be given

at school or daycare are needed, and the indigent family is spared the cost of an antibiotic prescription. The ED clinician need not worry about adherence. On the other hand, injections are associated with more severe allergic reactions, are painful, and are expensive, when one considers the cost of the medication and the nursing time to administer it.

Oral antibiotics are effective but must be taken several times daily for a long course, increasing the risks of nonadherence and only partially treated GABHS. Most authorities still recommend a 10-day course of most oral agents.¹⁰¹ However, several small randomized trials have indicated that either once- or twice-daily amoxicillin or twice-daily penicillin is an effective alternative to the standard schedule of 4 doses per day.¹⁰²⁻¹⁰⁴ Adherence with medication increases as the number of doses per day decreases, so regimens allowing fewer doses of medication each day are attractive. Furthermore, once- or twice-daily dosing eliminates the need for a child to take a dose of medication at school or daycare. While these results are promising, all these studies involved a relatively small number of subjects. A larger randomized trial is required before these treatment options can be considered the standard of care.

Recently, evidence has also surfaced that penicillin should not be the first-line agent for pharyngitis.^{xviii} In this meta-analysis involving 35 trials and 7125 subjects, the likelihood of treat-

Table 2. Recommended Antibiotics For GABHS Infections In Adults

Patients who ARE NOT allergic to penicillin:

Standard treatments

- Penicillin V: 250 mg PO every 6-8 hours for 10 days **OR**
- Penicillin G benzathine: 1.2 million units IM (1 dose)

Alternative treatments

- Penicillin V: 500 mg PO 2 times per day for 10 days **OR**
- Amoxicillin: 750 mg PO 1 time per day for 10 days*

Patients who ARE allergic to penicillin**:

Standard treatmentsⁱⁱ

- Azithromycin: 500 mg PO on day 1 followed by 250 mg PO on days 2-5; each dose is taken only 1 time per day **OR**
- Cefadroxil: 1000 mg PO 1 time per day for 10 days[†]
- Cephalexin: 500 mg PO 2 times per day for 10 days[†]

* Research supports this regimen; however, it is based on a few relatively small studies (**Class II**)

[†] Cephalosporins should not be used in patients with severe-type penicillin allergy

**Erythromycin may be a cheaper treatment.

For Class of Evidence descriptions, see page 1.

Abbreviations: IM, intramuscularly; PO, by mouth.

ment failure was statistically more significant with oral penicillin as compared with oral cephalosporins. The study also noted the disturbing trend of increasing treatment failure rate with oral penicillin over the past few decades.

To confuse the matter, a large Cochrane review published in early 2009 analyzed 20 studies that involved 13,102 patients over nearly 60 years. The results showed that 3 to 6 days of treatment with some of the "newer" oral antibiotics (eg, azithromycin [used in 6 studies] and first-generation cephalosporins) appeared to have been as effective in treating GABHS pharyngitis as was a 10-day course of oral penicillin.ⁱⁱⁱ The authors suggest that in regions with low rates of rheumatic fever, children with GABHS may be treated with a shorter course of antibiotics. However, the study does not compare a short course of antibiotics with intramuscular high-dose

Table 3. Recommended Antibiotics For GABHS Infections In Children

Patients who ARE NOT allergic to penicillin:

Standard treatments

Penicillin V:

- Patients < 27 kg: 125 mg PO 4 times per day for 10 days
- Patients ≥ 27 kg: 250 mg PO every 6-8 hours for 10 days **OR**

Penicillin G benzathine:

- Patients < 27 kg: 600,000 units IM (1 dose)
- Patients ≥ 27 kg: 1.2 million units IM (1 dose)

Alternative treatments

Penicillin V:

- Patients < 27 kg: 250 mg PO 2 times per day for 10 days
- Patients ≥ 27 kg: 500 mg PO 2 times per day for 10 days

OR

Amoxicillin:

- Patients < 27 kg: 40 mg/kg PO 3 times per day for 10 days
- Patients ≥ 27 kg: 750 mg PO 1 time per day for 10 days*

Patients who ARE allergic to penicillin**:

Standard treatmentsⁱⁱ

- Azithromycin: 10 mg/kg (maximum dose, 500 mg) on day 1 followed by 5 mg/kg (maximum dose, 250 mg) on days 2-5; each dose is taken only 1 time per day **OR**
- Cefadroxil: 30 mg/kg/day (maximum dose, 1000 mg) in 2 divided doses for 10 days[†] **OR**
- Cephalexin: 25-50 mg/kg/day (maximum dose, 500 mg) in 2-4 doses for 10 days[†]

* Research supports this regimen; however, it is based on a few relatively small studies (**Class II**)

[†] Cephalosporins should not be used in patients with severe-type penicillin allergy

**Erythromycin may be a cheaper treatment.

For Class of Evidence descriptions, see page 1.

Abbreviations: IM, intramuscularly; PO, by mouth.

penicillin. Several of the studies reviewed were also equivocal, and one might question the stringency of studies drawn from a 5-decade span of time.

While a short course of antibiotics has not yet been universally accepted, ED clinicians should note that there is ongoing interest in decreasing the overutilization of antibiotics in treating pharyngitis. They should be cognizant of future recommendations/protocols advocating for such an approach if more evidence is revealed through newer studies.

In addition to problems with adherence, oral medications are associated with some unwanted side effects. Gastrointestinal symptoms such as vomiting and diarrhea are not uncommon. Furthermore, many liquid medication preparations are rather unpalatable. It is difficult to force a struggling toddler to take a medication that he or she does not want. All these factors should be considered with the patient and/or patient's parents before a final decision regarding treatment is made.

The Role Of Tonsillectomy In Recurrent Pharyngitis

For patients with repeated episodes of pharyngitis, the ED clinician may refer them to an otolaryngologist, who would evaluate them for a possible tonsillectomy. Although the scope of that evaluation is beyond the scope of this chapter, ED clinicians should be aware that a large-scale Cochrane literature review suggests that adenotonsillectomy is effective at reducing the number of episodes of sore throats and well as the days with sore throat per episode in children.^{xix} This effect is 'modest' according to this and several other published studies. Researchers in these studies suggest that the benefit may be modest because recurrent pharyngitis often resolves spontaneously without surgical treatment. One study even suggests that when considering the cost and possible morbidity associated with the operation, tonsillectomy cannot be justified in most patients.^{xx}

Table 4. Other Agents Effective Against GABHS

Cefuroxime

- Adults: 250 mg PO 2 times per day for 10 days
- Children: 20 mg/kg/day PO in 2 divided doses for 10 days

Clindamycin

- Adults: 300-450 mg PO 4 times per day for 10 days
- Children: 20-30 mg/kg/day in 4 divided doses for 10 days

Amoxicillin/clavulanate

- Adults: 250-500 mg PO 3 times per day for 10 days
- Children: 40 mg/kg/day in 3 divided doses for 10 days

Abbreviation: PO, by mouth.

To avoid surgery, researchers are studying alternatives to these invasive procedures. For example, some have suggested chronic aerosolized antibiotic treatment in children with repeated pharyngitis^{xxi}; initial findings are promising, and results of definitive research are pending.

ED clinicians should therefore advise patients to consider tonsillectomy, with possible adenotonsillectomy, only after careful consultation with their primary care physicians and otolaryngologists.

Summary

The vast majority of patients who come to an ED for treatment of pharyngitis have a self-limited viral illness. These patients have a right to expect pain relief and education but do not necessarily require antibiotics. A substantial number of patients, particularly school-age children, will have an infection caused by GABHS. Finally, a small minority of patients will have a more serious underlying illness. A careful history and physical examination coupled with judiciously selected ancillary tests will identify most of these patients. The ED clinician must, as always, be vigilant to detect the few with serious illness among the many with routine pharyngitis.

Case Conclusion

Taking a deep breath, you calmly assured the patient and the mother that you would do your utmost to meet the patient's medical needs. Thankfully, you had recently perused the Emergency Medicine Practice article on "Pharyngitis in the ED" and were able to confidently proceed with your history and physical. The patient had several days of accompanying nasal congestion, conjunctivitis, and cough on history. You noted the patient appeared well, was afebrile, and had no airway compromise on examination. Her oropharynx were mildly injected but with no exudates. No lymph nodes were palpated. Satisfied that no further workup was needed, you gave thorough discharge instructions for a presumed viral syndrome. Additionally, you informed the patient and the parent that the rash may be an allergic reaction to the antibiotics and requested they inform all future care providers of the fact. Mollified by your careful history and physical examination as well as your patience with hearing the mother's frustration out, the patient and her

Table 5. Agents Not Effective Against GABHS

- Tetracyclines
- Fluoroquinolones
- Sulfonamides
- Trimethoprim
- Chloramphenicol

mother promised to give you excellent reviews in the survey. You were just happy that no time was spent on unnecessary testing as the waiting room seemed to be getting more crowded by the minute.

References

Evidence-based medicine requires a critical appraisal of the literature based on study methodology and number of subjects. Not all references are equally robust. The findings of a large, prospective, randomized, and blinded trial should carry more weight than a case report.

To help the reader judge the strength of each reference, pertinent information about the study, such as the type of study and the number of patients in the study, will be included in bold type following the reference, where available. In addition, the most informative references cited in this paper, as determined by the authors, will be noted by an asterisk (*) next to the reference number.

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Cost- And Time-Effective Strategies For Patients With Pharyngitis

1. **Do not test or prescribe antibiotics for patients with obvious viral syndromes.** Patients with cough, coryza, conjunctivitis, and other symptoms of viral illness are very unlikely to have concomitant GABHS infections. Treatment of such patients should be directed toward making them feel better.

Risk Management Caveat: This rule applies to otherwise healthy, immunocompetent patients who do not live in areas where rheumatic fever is endemic. More liberal treatment of high-risk patients is warranted.

2. **Do not perform throat cultures for GABHS in patients over 15 years old.** Adults are at lower risk for rheumatic fever and are at lower risk for severe complications should they have rheumatic fever. Therefore, most authorities recommend that adults be managed with a combination of clinical guidelines and RADTs.

Risk Management Caveat: See prior item.

3. **If you are going to treat based on clinical criteria, do not test.** Ordering a culture or RADT in a patient who has already received a prescription for antibiotics has no practical purpose.

4. **Limit the use of injections.** Injections ensure treatment and are appropriate in some cases, but for most patients a simple prescription is a less-expensive and equally effective alternative.

5. **Do not prescribe broad-spectrum, new, or advanced antibiotics to treat pharyngitis in patients who are not allergic to penicillin.** Penicillin or amoxicillin are effective in the treatment of GABHS infections. There is no evidence of GABHS resistance to these agents, and there is little reason to use more expensive antibiotics to treat pharyngitis in patients who are not allergic to penicillin. For penicillin-allergic patients, the problem is somewhat more complex. The cheapest agent available is erythromycin. However, there is a relatively high incidence of GABHS resistance to erythromycin. Furthermore, azithromycin requires a shorter treatment course and has a better safety profile. Therefore, azithromycin should be preferentially considered.

Risk Management Caveat: ED clinicians should prescribe treatment based on the community's bacterial resistance pattern.

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CME Questions

17. Conjunctivitis, cough, rhinorrhea, skin rash (other than scarlatina), and mucosal ulcers in patients with pharyngitis suggest that the diagnosis is likely to be:
 - a. GABHS
 - b. Viral pharyngitis
 - c. Epiglottitis
 - d. Ludwig's angina
18. Which of the following must be identified in the evaluation of patients with pharyngitis in order to rule out serious and/or life-threatening conditions?
 - a. Existing or impending respiratory compromise
 - b. Epiglottitis, retropharyngeal abscess, Ludwig's angina, peritonsillar abscess, or mononucleosis with severe tonsillar and lymphoid hypertrophy
 - c. Severe dehydration due to inability to drink
 - d. All of the above
19. Non-infectious causes of pharyngitis include smoke inhalation, thermal or chemical burns, swallowed objects, vocal strain, gastroesophageal reflux disease, thyroiditis, and malignancy.
 - a. True
 - b. False
20. In patients with intense throat pain but little inflammation of the tonsils and hypopharynx, which of the following is the most likely explanation?
 - a. Viral pharyngitis
 - b. GABHS
 - c. Epiglottitis
 - d. Peritonsillar abscess
21. According to several recent clinical guidelines, patients with pharyngitis with signs of a viral illness should be managed symptomatically without testing or treatment.
 - a. True
 - b. True for adults; false for children
 - c. True for children; false for adults
 - d. False
22. According to several recent studies about the use of clinical decision rules for children with pharyngitis, children who have a scarlatini-form rash associated with other typical symptoms of GABHS infection:
 - a. Can be treated presumptively
 - b. Should have an RADT and throat culture
 - c. Should be treated with chloramphenicol
 - d. Should have a throat culture and referral for follow-up

23. According to several recent clinical guidelines, the drug of choice for patients with GABHS is penicillin (or erythromycin/azithromycin for the penicillin-allergic).
- True
 - False
24. Which of the following, in conjunction with pharyngitis, most likely represents Ludwig's angina?
- Cough, rhinitis, conjunctivitis
 - Fever, dysphagia, trismus
 - Fever, lymphadenopathy, tonsillar hypertrophy
 - Fever, immunocompromise, recent dental trauma/dental disease
25. Which of the following, in conjunction with pharyngitis, most likely represents viral pharyngitis?
- Cough, rhinitis, conjunctivitis
 - Fever, dysphagia, trismus
 - Fever, lymphadenopathy, tonsillar hypertrophy
 - Fever, immunocompromise, recent dental trauma/dental disease
26. Which of the following, in conjunction with pharyngitis, most likely represents mononucleosis?
- Cough, rhinitis, conjunctivitis
 - Fever, dysphagia, trismus
 - Fever, lymphadenopathy, tonsillar hypertrophy
 - Fever, immunocompromise, recent dental trauma/dental disease
27. Which of the following, in conjunction with pharyngitis, most likely represents peritonsillar abscess?
- Cough, rhinitis, conjunctivitis
 - Fever, dysphagia, trismus
 - Fever, lymphadenopathy, tonsillar hypertrophy
 - Fever, immunocompromise, recent dental trauma/dental disease
28. Patients with symptoms of viral illness are unlikely to have concomitant GABHS infections. Therefore, testing and antibiotics are unnecessary.
- True
 - True, if the patient is otherwise healthy and does not live where rheumatic fever is endemic
 - True for children; false for adults
 - False
29. Which of the following is not one of the Centor criteria?
- History of fever
 - Absence of cough
 - Age less than 15 years
 - Swollen, tender, anterior cervical lymph nodes
 - Tonsillar exudate
30. According to CDC guidelines for pharyngitis in adults, patients with a Centor score of 4:
- Should be treated presumptively with antibiotics or tested with an RADT
 - Should not be tested or treated with antibiotics
 - Have a 2% chance of having GABHS
 - Should be treated with tetracycline
31. According to CDC guidelines for pharyngitis in adults, patients with a Centor score of 0 or 1:
- Should be treated presumptively with antibiotics or tested with an RADT
 - Should not be tested or treated with antibiotics
 - Have a 50% chance of having GABHS
 - Should be treated with fluoroquinolones
32. Which of the following has the least evidence to support its effectiveness in providing symptomatic relief for patients with pharyngitis?
- Over-the-counter analgesics like acetaminophen
 - Oral narcotic agents like hydrocodone
 - Antihistamines
 - Corticosteroids

HIV-Related Illnesses: The Challenge Of Emergency Department Management

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CME Objectives

Upon completing this article, you should be able to:

1. Assess a patient's risk of being infected with HIV, describe the importance of the CD4 count in determining the stage of infection, and evaluate the risk of infection with opportunistic pathogens.
2. Describe the most common CNS, gastrointestinal, and respiratory complications of HIV-associated disease as well as their proper evaluation and treatment.
3. Evaluate and manage the febrile AIDS patient.
4. Describe the most common side effects and toxicities of drugs used to treat HIV infection and AIDS.

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The triage note is innocuous enough—"fever for 1 week"—but when you walk into the room, you realize something else is going on. This young man is cachectic with thinning hair, and his spindly arms are crusted with an awful rash. As he speaks, you notice ominous white patches covering his tongue. His voice rasps, "Doc, can you help me? I think I have a virus."

Patients infected with the human immunodeficiency virus (HIV) present unique challenges for the Emergency Department (ED) clinician. Many are asymptomatic and are at no special risk for unusual diseases. However, those who progress to AIDS are susceptible to a wide range of both typically encountered and opportunistic infections. Furthermore, the therapies themselves are often associated with significant complications and morbidity in persons infected with HIV.

Many of those infected with HIV are unaware of their serologic status. For this reason, it is important to consider the possibility of HIV-related illness in anyone presenting with complaints suggestive of infection.

For patients known or suspected to have HIV infection, determining the degree of immunosuppression will help the ED clinician evaluate the risk for opportunistic disease. HIV-infected patients may report vague constitutional symptoms such as fever, weight loss, and fatigue. Others have complaints localized to a specific organ system or area — pulmonary, neurologic, abdominal, head and neck, dermatologic, or psychiatric.¹ Infections of the lung and central nervous system (CNS) are the most common illnesses identified in HIV-positive patients who present to the ED.

Because AIDS-related infections tend to present atypically or with subtle findings, a high index of suspicion and an aggressive approach to diagnosis

are crucial for successful management. Although AIDS-related infections often cannot be cured, many can be successfully treated in the short term, and perhaps controlled over the long term, using suppressive therapy.

Clinicians may be intimidated by the daunting array of diseases associated with HIV infection, as well as by the dizzying pace of new developments. But fear not! This article is intended to provide indispensable insights about how to manage the common complications of HIV infection seen in the ED.

Epidemiology

The earliest known HIV infection was discovered in a stored blood plasma sample dating from 1959. The victim, from Leopoldville (now Kinshasa), in the Democratic Republic of Congo, puzzled local physicians with his symptoms. While they were unable to save him, they did save his blood—which decades later proved to harbor HIV.² Computer models suggest that the epidemic may have begun in central West Africa around 1930.³ The early origins of human infection are shrouded in controversy; one theory suggests transmission of a simian AIDS virus via cuts on the hands of human hunters, while another suggests unsanitary immunization practices.^{4,5}

The first report of AIDS in the United States was in June of 1981 and involved 5 cases of unexplained immune deficiency in homosexual men in Los Angeles. From there, the epidemic exploded until, by the end of 2000, 774,467 Americans had met the case definition for the disease. In 2000, the Centers for Disease Control and Prevention (CDC) estimated that 650,000-900,000 Americans were infected with HIV, and over 320,000 had AIDS.⁶ At the end of 2003, according to the CDC, an estimated 1,039,000 to 1,185,000 persons in the US were living with HIV/AIDS.¹ The CDC es-

estimated in 2006 that there would be 56,300 new cases, both diagnosed and undiagnosed.

The dynamic of the epidemic has changed dramatically since the advent of highly active anti-retroviral therapy (HAART), which includes protease inhibitors and other new agents in multidrug regimens. Although the rate at which new cases of HIV infection come to light has remained steady at about 40,000 per year, the death rate has dropped significantly (declines of 50% in 1997 and 21% in 1998).^{7,8} This decrease in mortality has held steady in the first decade of the 21st century. Yet for some segments of the population, particularly Hispanics and African-Americans, the rates of infection are increasing. In 2006, the CDC found that although African-Americans make up only 13% of the population, they account for almost half the diagnoses.ⁱⁱ Heterosexual contact is the fastest-growing category of HIV transmission in the US.

The local prevalence of HIV infection may vary widely, from nearly 0% in some rural locales to over 10% in some inner-city hospital EDs, with an average of 0.56% for the US population as a whole.^{9,10} The prevalence of HIV seen in the ED is steadily growing. A retrospective study conducted in 2 urban hospitals indicated that at least 4% of patients who presented to the ED were HIV-seropositive and 14% of all admissions were found to be seropositive. Since an unspecified number of patients are not aware of their HIV status, the prevalence of HIV-seropositivity in the ED is probably even higher.ⁱⁱⁱ

Pathophysiology And Natural History

Initial Response To HIV

The mechanism for immune destruction by HIV is complex and remains the focus of intense investigation. The virus gains entrance into the target cell after binding with the CD4 receptor and 1 of several chemokine receptors. Complex protein interactions fuse the viral capsule and the cell membrane.¹² Although the CD4+ T lymphocyte (also known as the T helper cell) is the primary target, any cell expressing this receptor is susceptible to infection.

During the first 4 to 6 weeks of infection, the number of viral particles soars, and the virus disseminates throughout the circulation and lymphoid tissue. It is estimated that 55% to 92% of patients experience the acute retroviral syndrome — a mononucleosis-like illness characterized by fever and generalized lymphadenopathy. Patients may also develop pharyngitis, rash, myalgias, headache, nausea, and diarrhea.^{13,14}

As the body generates an immune response to the virus, the viral load falls and a variable period of clinical latency ensues. During this stage, the CD4 count exceeds 500/mm³. Opportunistic infections are rare, but patients may present with general-

ized lymphadenopathy or aseptic meningitis. The latency period may last 2 to 10 years or more, but despite the paucity of symptoms, levels of CD4+ cells decline. This depletion is due to both virus-mediated cell destruction and inhibition of normal T cell production.¹⁵ Eventually, the loss of CD4+ cells and the resulting immunodeficiency permit infection from an opportunistic pathogen. At this stage of HIV infection — defined as AIDS — the viral load climbs steadily, and in the absence of therapy, clinical decline is inexorable. Once this stage is reached, the median survival is 9 to 12 months if the patient remains untreated.^{16,17}

“Fear and ignorance about AIDS can so weaken people’s senses as to make them susceptible to an equally virulent threat: bigotry.”

—“AIDS and the New Apartheid,”
New York Times Editorial, October 7, 1985

Specific CD4 Levels

A patient with a reduced CD4 count of 200 to 500/mm³ may develop lymphadenopathy, oral candidiasis, idiopathic thrombocytopenic purpura, or hairy leukoplakia. This stage also predisposes the patient to more virulent pathogens, such as *Mycobacterium tuberculosis* or *Streptococcus pneumoniae*.¹⁸ Antiretroviral drugs are generally indicated for this degree of immunosuppression.

A CD4 count less than 200/mm³ leads to more advanced disease. It is important to identify patients in this category, because they are at much higher risk of opportunistic infections, including *Pneumocystis pneumonia* (PCP), tuberculosis (TB), toxoplasmosis, cryptosporidiosis, isosporiasis, esophageal candidiasis, cryptococcosis, and histoplasmosis. [Note: although the name of the *Pneumocystis carinii* bacterium has changed to *Pneumocystis jiroveci*, the disease is typically referred to as “PCP.”] Disseminated *Mycobacterium avium* complex (MAC) or cytomegalovirus (CMV) infection tend to occur in patients with CD4 counts below 50/mm³.

Patients who report a previous opportunistic infection have, at some point, reached a critical CD4 nadir. At this stage they require both antiretroviral therapy and prophylaxis against opportunistic infections. An exception to this, however, is those in whom immune reconstitution has been successful — that is, their CD4 count has risen to above 200/mm³. Such patients will continue antiretroviral therapy but may discontinue PCP prophylaxis.^{19,iv}

Prehospital Care

The response of emergency medical service (EMS) units to a patient with HIV infection or AIDS should be no different than for an uninfected individual. Usually, the EMS personnel will be unaware of the

patient's serologic status (as might the patients themselves). EMS personnel should wear gloves and place a mask on patients who have a cough. Very little literature has been published that directly addresses prehospital care of the HIV-infected patient.

ED Evaluation

History

One of the most valuable questions an ED clinician can ask when faced with a febrile patient who has a cough or constitutional symptoms is: "Have you ever been tested for the AIDS virus?" Up to 30% of HIV patients may not spontaneously disclose such information when seeking medical care.²⁰ On the other hand, many HIV-infected people in the US are unaware of their serologic status. Unrecognized HIV infection is common in the ED, especially among women and the elderly.^{21,22} A recent published study also found that subjects who were higher risk for HIV based on sexual preference (such as men who have sex with men [MSM]) were reluctant to disclose such behavior even when asked about it by their own physicians.^v Blacks and Hispanics were more reluctant than whites to report their behavior to their physicians. Amazingly, a small percentage of patients who claim to have AIDS may, in fact, be HIV-negative. The deception may be engineered in order to receive preferential treatment with regard to housing, disability payments, prescription drugs, or medical care.²³

Factors associated with an increased risk of HIV infection include men who have sex with men, injection drug use, prostitution, heterosexual exposure to a partner at risk, and exposure to a blood product in the US prior to 1985. Children born of mothers in such groups are also at risk. Because the number of people who fall into 1 or more of the high-risk groups is still a fairly small proportion of the general population, identification of risk factors remains important. However, as the epidemiology of HIV transmission continues to evolve and heterosexual transmission becomes more common, risk factor determination may become less useful.

ED clinicians should question patients about HIV risk factors if they present with signs and symptoms suggestive of infectious disease, especially respiratory illness, fever, headaches, diarrhea, and rashes. Possible risk factors in sexual partners are germane. Although some patients may hesitate to answer questions about such personal matters as sexuality and drug use, most will make an honest disclosure when questions are asked in a straightforward, nonjudgmental manner.²⁴

If HIV infection is known or suspected, the next step is to try to determine the stage of the disease. The expected complications of HIV infection vary depending on the phase of the infection, and the ED

clinician should inquire about prior hospitalizations or complications. (See Table 1.)

In the evaluation of patients known to be seropositive, the CD4 count can provide valuable insight into the stage of HIV disease and the risk of opportunistic infection. Any patient who reports a previous opportunistic infection has, at some point, had a CD4 count below 200/mm³. Some patients may be able to report their latest CD4 count and when it was obtained. Those less medically sophisticated or lacking ready access to medical care may have no idea about their CD4 count. If the patient is receiving regular medical care, the list of medications may also suggest the stage of his or her disease.

Physical Examination

In addition to a careful and compassionate history, an appropriate physical examination is essential. The only study to address the sensitivity of the physical examination to detect HIV infection was conducted among infants.²⁵ However, cohort studies show that certain physical findings provide important clues to HIV-related infections.

Many patients in the advanced stages of AIDS can be identified by a "doorway diagnosis." Look to the general appearance of a patient for specific indications. Wasting (malnutrition) and lipodystrophy (caused by a combination of antiretroviral therapy, the infection itself, and immune reconstruction due to therapy) are the 2 major nutritional alterations in HIV infection, and temporal wasting and parietal hair loss are common manifestations.²⁶ Recent studies suggest that the wasting and lipodystrophy are reversible, but treatment is expensive and may be prohibitive for many HIV-infected persons.^{vi}

Before embarking on the physical examination, the ED clinician should determine whether the patient is in respiratory distress and take appropriate steps to alleviate this problem.

During the oral examination, pay special attention to the presence of candidiasis or hairy leukoplakia, because in a patient with a fever these findings would suggest an HIV-related illness. Patients with oral lesions tend to have low CD4 counts and rapid progression of the disease (especially when they

Table 1. Staging Of HIV Disease

Stage	Clinical Appearance	CD4 Count
Acute	Mono-like syndrome	Normal
Early	Asymptomatic or lymphadenopathy, aseptic meningitis, skin disease	> 500/mm ³
Middle	Asymptomatic or lymphadenopathy, thrush, idiopathic thrombocytopenic purpura, hairy leukoplakia	200-500/mm ³
Late	Opportunistic infections, malignancy, dementia, wasting	< 200/mm ³

remain untreated).^{27,28} Thrush does not necessarily equal AIDS; however, other causes for oral candidiasis include uncontrolled diabetes, recent antibiotic or inhaled steroid use, and chemotherapy.

While the lung examination may reveal rales or other signs of pulmonary disease, many patients with PCP pneumonia will have clear breath sounds. In addition to traditional auscultation, there is another useful test known as *auscultatory percussion*. To perform this maneuver, place the diaphragm of the stethoscope on the posterior chest of the patient, and lightly tap the manubrium with the tip of the index or middle finger. Compare the sounds in opposite sides of the posterior chest, taking care that the stethoscope is placed in the same interspace on the right and left sides. Differences in the quality, pitch, duration, or intensity of breath sounds suggest lung pathology. In 1 study of HIV-positive patients, auscultatory percussion was more predictive (sensitivity = 51.0%-69.6%) of chest x-ray abnormalities than was standard percussion or traditional auscultation.²⁹ However, the physical examination should be conducted with the knowledge that the traditional chest physical examination is highly inaccurate in the detection of pneumonia even in HIV-seronegative patients.^{vii} In addition, these studies were conducted in ideal conditions away from the sometimes chaotic environment of the ED. Therefore, the most reasonable approach to the HIV-positive patient with a pulmonary complaint is auscultation, after which a chest film should be obtained regardless of the physical findings.

Other notable findings include generalized lymphadenopathy, Kaposi's sarcoma (raised, purplish skin lesions), severe persistent dermatosis, and "track marks" from injection drug use. Seborrheic dermatitis, onychomycosis, herpes simplex, widespread scabies, alopecia, and rashes from systemic mycoses are common in HIV disease. Any underlying chronic dermatologic condition (eg, psoriasis, seborrhea, eczema) may become exacerbated as immunosuppression progresses. Both HIV infection and the medications used to treat it may cause neuropathy, manifested as sensory loss or abnormal reflexes.

Primary HIV Infection

Some believe it is important to diagnose acute retroviral syndrome because intervention with antiretroviral treatment during this stage may improve the long-term course of HIV infection. However, this improvement seems to be short-lived.^{30,31} As previously mentioned, 55% to 92% of patients initially exposed to HIV experience the acute retroviral syndrome, a mononucleosis-like illness with fever and generalized lymphadenopathy. In patients with more severe symptoms at the time of seroconversion, the disease

progresses more rapidly.³² Patients who present with compatible symptoms may be questioned about HIV risk factors, and those with likely exposure should be tested or referred for testing.

The HIV antibody test that is usually done to diagnose HIV infection is typically negative during the acute retroviral stage (the standard ELISA test requires a mean of 27 days after exposure to become positive).³³ Diagnosis at this stage would require testing for the p24 antigen or detecting HIV viral RNA directly. Not every patient with nonspecific viral symptoms warrants p24 testing. Determining which patients are at sufficiently high risk depends on the results of the history and physical examination. What is imperative, though, is educating the patient about the benefits of early testing involving HIV/AIDS.

"AIDS was ... an illness in stages, a very long flight of steps that led assuredly to death, but whose every step represented a unique apprenticeship. It was a disease that gave death time to live and its victims time to die, time to discover time, and in the end to discover life."

— Hervé Guibert, French writer (1955–1991)

Fever In HIV-Infected Patients

Etiology Of Fever In HIV-Infected Patients

HIV-infected patients commonly present with fever, which can pose a diagnostic challenge for the ED clinician. The differential diagnosis in such cases is broad and includes potentially life-threatening infections.³⁴ (See Table 2.) In addition, in this era of globalization and ease of international travel, disease entities usually seen in the more remote areas of the planet must be considered.^{viii}

Fever is common in the patient who is HIV-seropositive. In 1 prospective study of 176 patients with advanced HIV, almost half had an episode of fever over a 9-month period, and a specific etiology for the fever was determined in 83% of these cases. Lung infection accounted for more than 25%, while CNS infection accounted for more than 10%. Other common etiologies included disseminated MAC, peripherally inserted central catheter line infection, sinusitis, and drug reaction. (See Table 2.) When the patients' fever required more than 2 weeks to diagnose, the most common etiologies were lymphoma, *Mycobacterium avium-intracellulare* bacteremia, and PCP.³⁵

History And Physical Examination For HIV-Infected Patients With Fever

The history and physical examination will provide important clues to the etiology of the fever. First, determine how long or how often the patient has had fever. Prolonged fever is less likely to represent a treatable emergency. Ask about cough or shortness of breath. A new or worsening headache or neuro-

logic deficit in the HIV-positive patient with a low or unknown CD4 count suggests a CNS infection. Some constellation of nasal congestion or discharge, headache, and/or sinus tenderness may presage sinusitis, a common infection in the HIV-infected patient.³⁷ Most patients with significant intra-abdominal disease will have both abdominal pain and tenderness. Back pain or tenderness in the HIV-infected patient may reflect endocarditis (especially in IV drug users), urinary tract infection (UTI), or a spinal infection or neoplasm.^{38,39} Flank pain may also result from kidney stones, especially in patients taking indinavir. Patients with fever and extremity pain or tenderness may have pyomyositis⁴⁰ or, in the case of a painful joint, septic arthritis.

Not all fever equals infection, however. HIV-positive patients with fever may be suffering from a drug reaction. Hyperthermia, tachycardia, and tachypnea may be manifestations of a variety of drug effects, including neuroleptic malignant or anticholinergic syndrome, serotonin crisis, malignant hyperthermia, heatstroke, and aspirin or sympathomimetic agent overdose. HIV infection is a known risk factor for neuroleptic malignant syndrome and should be considered in all seropositive patients who take an implicated antipsychotic medication, especially if they present with fever and some combination of cogwheeling, diaphoresis, disorientation, or rigidity.³⁶

The antiretroviral drug abacavir can cause a hypersensitivity reaction characterized by malaise, fever, and nausea, with or without vomiting. The HLA-B*5701 allele was found to play a strong role in this hypersensitivity reaction. In a recent study in a control group given abacavir who were not screened for the allele, the prevalence of the hypersensitivity reaction was 7.8%, indicating that ED clinicians are likely to encounter this phenomenon.^{ix} In such cases, the drug must be stopped and never restarted, since the reaction may be fatal.¹⁶¹

Table 2. Common Etiologies Of Fever In AIDS Patients

- *P jiroveci* and other pneumonias
- Disseminated *M avium* complex infection
- Lymphoma
- Infection of indwelling central lines
- Sinusitis
- Toxoplasmosis
- Cryptococcal meningitis
- Salmonellosis
- Tuberculosis
- Drug reactions
- Bacteremia/sepsis
- Cytomegalovirus

Diagnostic Studies For HIV-Infected Patients With Fever

The findings on history and physical examination provide the basis for additional diagnostic studies. Obtaining blood tests seems to be a reasonable approach to fever in the patient with AIDS, but the data are often slim. In particular, the value of the CBC in management of suspected or known complications of HIV infection remains unknown. One study (published only in abstract form) showed that a high band count predicted positive blood cultures in HIV-positive patients.⁴¹ If a CBC is obtained, recognize that HIV infection alone may induce eosinophilia.⁴² Studies do show that neutropenia is strongly associated with risk of severe infections in those with end-stage AIDS⁴³ and, in particular, is linked to pseudomonal bacteremia.⁴⁴ One cohort study found that the rate of bacteremia due to *Escherichia coli*, *Klebsiella pneumoniae*, or *Pseudomonas aeruginosa* is increased eightfold when the absolute neutrophil count is less than or equal to 500/mm³. However, in this study, the absolute neutrophil count was measured in a routine blood test the week before bacteremia developed, not during the acute event.

CBC To Estimate CD4 Counts

The CD4 count is one of the best predictors of risk for an opportunistic infection. In general, it is not feasible to obtain a CD4 count within the time frame of an ED evaluation, but fortunately the absolute lymphocyte count (ALC) may be used as a surrogate marker. The ALC can be calculated using data provided by the CBC and differential blood count as follows:

$$\text{ALC} = \text{total white blood cell count} \times \text{lymphocyte percentage}$$

Two studies performed in a clinic setting (ie, not the ED) showed a good correlation between the CD4 count and ALC.^{45,46} On the other hand, these 2 studies are not necessarily applicable to the ED population, since all the participants were tested during routine examinations, not while they were acutely ill.

In a third study, a retrospective investigation from Temple University, involved 807 blood samples from HIV-positive patients.⁴⁷ Both a CD4 count and a CBC with differential were ordered, with the latter samples drawn in a variety of settings, including clinics, inpatient wards, and EDs. Although a single ALC threshold was neither sensitive nor specific for a low CD4 count, the investigators determined 2 valuable cut-off points: an ALC less than 1000/mm³ was 91% predictive of CD4 counts below 200/mm³ (sensitivity only 67%, but specificity 96%), while an ALC greater than 2000/mm³ was 95% predictive of CD4 counts greater than 200/mm³. The authors

concluded that patients with an ALC greater than 2000/mm³ might be less susceptible to opportunistic infections, while those with an ALC less than 1000/mm³ are at higher risk.⁴⁷ Unfortunately, these researchers had no access to clinical data and could not account for confounding factors such as anti-retroviral therapy or the presence of acute infection such as sepsis, pneumonia, or TB.

Blood Culture And Urine Tests

Because of the possibility of bacteremia with *S pneumoniae*, *Salmonella* sp, or other organisms, some have suggested that blood cultures be performed in the febrile patient with HIV infection, but the value of this approach is not known. Blood cultures may be useful in diagnosing unsuspected MAC disease in those with low CD4 counts.⁴⁸ High-risk subgroups that may benefit most from blood cultures include patients who appear toxic, injection drug users, those with signs of bacterial endocarditis (especially a new heart murmur), those with a central venous catheter, persons with very low CD4 counts (< 50/mm³), and patients with neutropenia and fever. One study showed that bacteremia in young HIV-infected children was associated with temperatures of 39°C (102.2°F) or greater, a WBC count of 15,000/mm³ or greater, and the presence of a central venous catheter.⁴⁹

Dipstick or microscopic evaluation of the urine is indicated in patients with urinary symptoms or flank or lower abdominal pain. Because women in general have more UTIs than men, some ED clinicians regularly examine the urine in women with HIV who have no obvious source for their fever. However, routine urinalysis might also be valuable in the febrile man with advanced HIV disease. One study showed that HIV-infected men with CD4+ cell counts less than 200 × 10⁶/L are at increased risk for bacteriuria,⁵⁰ while another found that half of male AIDS patients with a UTI had no urinary symptoms.⁵¹

Radiographic Studies For HIV-Infected Patients With Fever

Some authorities recommend chest radiography in all HIV-infected patients who have fever without a known source. They argue that because the symptoms of PCP are often subtle in its early stages, chest radiography may detect occult pneumonia.⁵² They further suggest that tests such as exercise pulse oximetry and serum lactic dehydrogenase (LDH) should be considered even if the patient lacks significant respiratory symptoms.⁵³

More recently, serum markers such as beta-D-glucan were found to be reliable diagnostic markers for PCP.^x A follow-up study indicates that there was also a statistical improvement in diagnosis, especially in patients with HIV seropositivity. However, this follow-up study was a retrospective chart review involving only 35 patients.^{xi} Regardless of these

recent findings, a chest radiographic study is still the standard of care in febrile HIV-seropositive patients with fever of unknown origin.

Because CNS infection is a common cause of fever, head computed tomography (CT) and lumbar puncture (LP) should be performed in AIDS patients with unexplained fever who complain of headache or neurologic symptoms. Neurologic deficits or meningeal signs are not prerequisites for neuroimaging or LP, since HIV patients with focal lesions often lack focal findings, and cryptococcal meningitis typically presents without classic meningeal findings.^{54,55} If the patient has a nasal discharge or sinus tenderness, consider a CT scan of the sinuses in addition to the head CT.

Echocardiography is a reasonable imaging procedure for the HIV-positive patient with a murmur, especially if the murmur is new. A recent history of IV drug abuse significantly raises the likelihood of a positive result.^{56,57}

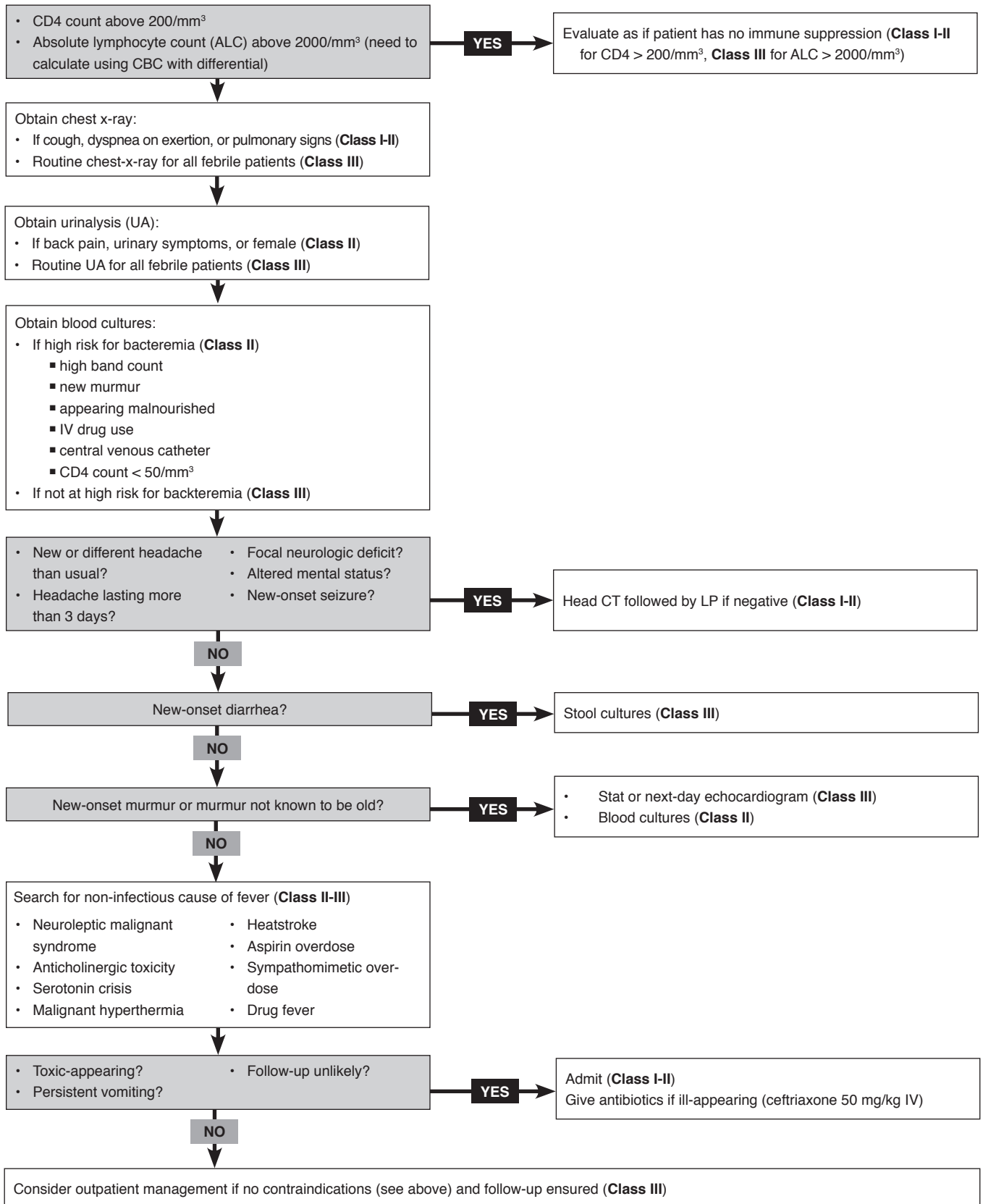
Disposition Of HIV-Infected Patients With Fever

There are no robust studies that tell us which febrile HIV-infected patients require admission to the hospital. According to a retrospective study done almost 2 decades ago, the only reliable factors that predict the need for admission are the presence of dyspnea, cough, and fever with an abnormal chest radiograph.^{xii} However, the small number of patients involved in this study raise questions about the validity of these results in current clinical practice. Nevertheless, it is generally accepted that patients with unexplained fever who appear acutely ill should be admitted to the hospital for further work-up. Those who do not appear acutely ill can be sent home provided that close follow-up can be arranged with a primary care provider, who should review results of tests such as blood cultures for bacteria and MAC.

Respiratory Complaints In HIV-Infected Patients

The lungs are the most common site of serious infection in patients with AIDS, and historically *P jiroveci* has been the most common opportunistic pathogen. Because of PCP prophylaxis, the disease appears to be occurring less frequently and at a more advanced stage of AIDS.⁵⁸ HIV-infected individuals are also at increased risk for community-acquired bacterial pneumonia caused by *Streptococcus pneumoniae*, *H influenzae*, and other bacteria.⁵⁹ In fact, *S pneumoniae* continues to be the leading cause of pneumonia. With the advent of HAART, pneumococcal prophylaxis for those with CD4 counts below 200/mm³, and PCP prophylaxis, the prevalence of pneumonia in

Clinical Pathway For Evaluation Of The HIV-Positive Patient Who Has Fever Without A Source*



*Give antibiotics emergently if signs of toxicity or sepsis - before obtaining diagnostic studies. (May draw blood cultures if done expediently.)

For Class Of Evidence Definitions, see page 1.

HIV-seropositive patients may be halved.^{xiii}

Mycobacterium tuberculosis should also be considered in all HIV-infected patients with pneumonia, and it often presents atypically in these patients. Fungi such as *Cryptococcus neoformans*, *Histoplasma capsulatum*, and *Coccidioides immitis* are less frequent culprits. Occasionally a malignancy such as Kaposi's sarcoma or lymphoma can be mistaken for pneumonia.⁶⁰

Early Isolation Procedures For HIV-Infected Patients With Respiratory Complaints

Although both the risk factors for and symptoms of TB are usually present in HIV-infected patients, the opportunity to isolate those with TB is often missed at triage.⁶¹ If a patient complaining of shortness of breath or cough and fever is believed (or known) to have HIV infection and/or a low CD4 count, the triage nurse should place him or her in respiratory isolation. Early isolation may protect both the ED staff and other patients from contagion.⁶² Many nosocomial outbreaks involve multidrug-resistant strains of TB, which result in high mortality rates among those infected.^{63,64} TB control measures such as respiratory isolation rooms, non-recirculated air, and droplet shields will reduce the spread of TB to ED personnel.⁵²

History And Physical Examination For HIV-Infected Patients With Respiratory Complaints

The evaluation of an HIV-infected patient with respiratory symptoms is similar to that of patients from the general population. (See the Clinical Pathway For Evaluation Of Respiratory Complaints In HIV/AIDS Patients, page 68.) In addition to taking the "usual" history, the ED clinician should consider the patient's level of immune impairment, prior exposure to infectious agents, and use of prophylactic therapy.

Pneumocystis Pneumonia

Whenever a patient at high risk for HIV infection presents with pneumonia, the ED clinician should suspect *P jiroveci* as the infecting agent. The classic presentation of PCP is subacute: patients complain of fatigue, fever, and malaise associated with dry cough. Dyspnea is common, especially on exertion. Some present to the ED with progressive dyspnea, having been recently and unsuccessfully treated for bacterial pneumonia by their primary care physician. PCP is typically seen in HIV-infected patients with CD4 counts below 200/mm³ and who may or may not have other markers of immunosuppression, such as Kaposi's sarcoma, lymphoma, oral candidiasis, weight loss, or dementia.

In some cases, looking in the mouth may be more fruitful than auscultating the lungs in patients with cough. The presence of oral candidiasis in any

patient with dyspnea suggests PCP (odds ratio = 2.6).⁵³ Prophylactic therapy with trimethoprim-sulfamethoxazole (TMP-SMX) or dapsone does not rule out the possibility of PCP, since about one-fifth of compliant patients will suffer breakthrough infections. PCP will also develop in nearly one-third of those using aerosolized pentamidine.⁶⁵

Tuberculosis (TB)

Another pathogen to consider is *Mycobacterium tuberculosis*. Between 1985 and 1992 the incidence of TB in the US rose by 18%, largely because of the AIDS epidemic. Fortunately, this was followed by a comprehensive strengthening of control measures that led to the lowest incidence of TB in US history by the year 2000.⁶⁶

Not only are AIDS patients more likely to become infected with TB, but their latent *M tuberculosis* infections are also more likely to progress to active disease.⁶⁷ Whereas the risk of progression to active TB in a patient without immunosuppression is about 5% to 10% over that person's lifetime, the risk for someone infected with HIV may be as high as 8% per year.⁶⁸ Because *M tuberculosis* is presumably more virulent than *P jiroveci* or other opportunistic infections, it tends to occur at an earlier stage of HIV infection.⁶⁹

The most common symptoms associated with pulmonary TB (chronic cough, hemoptysis, weight loss, and night sweats) may be absent or subtle in HIV infection.⁷⁰ Patients with active pulmonary TB frequently require multiple ED visits and often present with nonpulmonary complaints.

Diagnostic Studies For HIV-Infected Patients With Respiratory Complaints

Chest Radiography For HIV-Infected Patients With Respiratory Complaints

A chest film should be obtained in any patient with known or suspected HIV infection who presents to the ED with new respiratory symptoms. Although the "classic" findings may be absent for each of the 3 major categories of HIV-related pneumonias—PCP, community-acquired bacterial pneumonia, and TB—the chest x-ray is still a logical first step toward a diagnosis. The ED clinician must recognize that the radiographic findings of pneumonia are highly variable in HIV disease. Some patients may demonstrate single or multiple pulmonary nodules. In 1 study of 87 patients, the underlying etiology of pulmonary nodules was found to be opportunistic infections in 57 patients, bacterial pneumonia in 30, and TB in 14.⁷¹

The classic chest x-ray finding in PCP involves a diffuse interstitial infiltrate, which typically appears in a bilateral pattern that may be described as "granular," "reticular," or "ground glass."⁷² But the findings vary widely and can include lobar or nodular infiltrates, hilar lymphadenopathy, spontaneous pneumothorax, cavitation, and, rarely, pleural effu-

sions.⁷³ Apical infiltrates are often seen in patients taking prophylactic aerosolized pentamidine.⁷⁴ The chest film may also be normal, especially during early PCP.⁷⁵ Remember, PCP cannot be reliably distinguished from bacterial pneumonia or TB based on symptoms or findings on chest x-ray.

Although bacterial pneumonia often presents as a lobar infiltrate in the immunocompetent patient, it may exhibit atypical radiographic findings in the HIV-infected patient. With immunosuppression, traditional bacteria may produce diffuse interstitial infiltrates that are frequently misdiagnosed as PCP. In 1 review of HIV-infected patients with bacterial pneumonia, 47% had chest x-ray findings indistinguishable from the “classic” appearance of PCP.⁷⁶ A recent study from Italy echoed the findings above. For example, interstitial changes were seen in 17% of the patients who had isolates of *Streptococcus pneumoniae*, HAART did not significantly influence the radiographic appearance of lung diseases caused by pneumococcus, and the degree of immunosuppression correlated strongly with atypical presentations on the chest radiographic studies.^{xiv}

Although apical cavitory lesions are traditionally associated with TB, pulmonary cavities are rare in patients with AIDS who have TB, particularly in cases of long-standing immunosuppression. In 1 study of such patients only 6% had “typical” chest x-ray findings.⁷⁷ More common findings included hilar or mediastinal adenopathy or an infiltrate suggestive of pneumonia. About 35% of those with TB had no infiltrate, while 12% had a normal chest x-ray.⁷⁷

Children with AIDS may demonstrate a dramatic finding on chest radiography consisting of diffuse ground-glass opacities known as lymphoid interstitial pneumonitis.

Laboratory Studies For HIV-Infected Patients With Respiratory Complaints

Laboratory analysis can sometimes be helpful in HIV-infected patients with respiratory complaints, especially in patients with PCP. In PCP, arterial blood gas measurements often demonstrate hypoxemia with a marked increase in the alveolar-arterial (A-a) oxygen gradient. Because the degree of hypoxia and the size of the gradient have treatment implications (as described later), measuring arterial blood gases is useful when PCP is suspected.

Pulse oximetry may be normal or near normal in PCP, especially early in the disease. Exercise-induced desaturation is much more predictive of PCP than is resting hypoxemia (odds ratio = 4.88 vs 0.69; positive pressure ventilation = 77% vs 66%, respectively).⁷⁸ In 1 study of 45 AIDS patients with pneumonia, subjects were asked to pedal for 2 minutes on a stretcher bed.⁷⁹ In patients with PCP, the SaO₂ usually fell by 3% or more, but in those with non-PCP pneumonia it increased slightly with exercise. Sensitivity was

77% and specificity 91%. Since bicycles mounted on stretchers are rarely available to the ED clinician, having the patient do jumping jacks or jog in place would be a suitable alternative.

Several studies have found that elevated lactate dehydrogenase (LDH) suggests PCP.^{80,81} Although in patients with dyspnea an elevated LDH is a sensitive test, it is nonspecific (sensitivity 94% and specificity 78% for LDH > 220 IU/L).⁸² A normal LDH level does not rule out the diagnosis of PCP, but it does make it unlikely; in 1 study, only 7% of 84 patients with PCP had normal LDH levels.⁸³ A more recent study suggests that LDH is a good marker of organ damage rather than a specific marker of a particular disease process.^x Interestingly enough, in a retrospective review of reports published close to 20 years ago, the authors of this recent Japanese study found similar results supporting their claim. The evidence demonstrating that LDH was elevated not just in PCP but also in disseminated tuberculosis and bacterial pneumonia suggests the nonspecificity of the LDH level in PCP.^{xv}

The gold standard for diagnosing PCP is finding the organism on induced sputum samples or in samples from bronchoalveolar lavage using special stains. Because of the increased risk of TB in AIDS patients, sputum induction should not be done in the ED unless proper isolation facilities are available. Therefore, in the emergency practice, a high degree of suspicion of an infectious etiology in respiratory complaints based on history and physical examination, along with supporting radiographic and laboratory data, is imperative for proper diagnosis and treatment.

Treatment Of HIV-Infected Patients With Respiratory Complaints

Since neither the radiographic findings nor the laboratory findings can reliably distinguish the pathogen in HIV-related pneumonia, how does an ED clinician choose the right therapy? Although clues in the patient’s presentation and laboratory results may suggest a particular etiology, a safe approach is to address all the most common pathogens — PCP, community-acquired bacterial pneumonia, and TB — in each patient.

To a significant extent, treatment will depend on the severity of illness, which begs the question, “When should patients with suspected PCP be admitted?” Studies show that certain factors predict a poor outcome⁸⁴⁻⁸⁶:

- increased LDH
- PO₂ less than 70 mm Hg
- wide A-a gradient (usually associated with a low PCO₂)
- abnormal chest film
- previous admission for PCP
- rales on chest examination

Certain patients with these findings — especially those who appear toxic — and those with persistent vomiting should be admitted to the hospital for further work-up. Those without reliable follow-up should also be admitted. (See also the September 1999 issue of *Emergency Medicine Practice*, “Community-Acquired Pneumonia: Deciding Whom To Admit And Which Antibiotics To Use.”) When opting for outpatient treatment, it is important to collaborate with the patient’s primary care physician.

Oral Therapy For HIV-Infected Patients With Respiratory Complaints

Although many patients diagnosed with PCP will need to be admitted, some of those with mild illness can be managed as outpatients if close follow-up is available. Oral TMP-SMX is preferred for outpatient therapy; the usual dosage is 2 double-strength tablets given 3 times a day for small adults or 4 times a day for larger adults for 21 days. Other oral treatment options include trimethoprim plus dapsone or clindamycin plus primaquine.⁸⁷ Patients who are HIV-seropositive usually respond to treatment later than those who are HIV-seronegative (ie, within 4 to 5 days), but improvement should still be seen within 8 days. ED clinicians should also instruct patients that up to 10% of mild-to-moderate cases of PCP fail to respond to antibiotic therapy.

Intravenous Therapy For HIV-Infected Patients With Respiratory Complaints

For patients being admitted to the hospital, initiating therapy in the ED can help avoid delays that can occur if therapy is started after arrival on the ward. The drug of choice is intravenous TMP-SMX. The usual regimen is 15 to 20 mg/kg/d (based on the trimethoprim) in 4 divided doses, to be continued for 21 days. TMP-SMX is supplied in ampules containing 80 mg of trimethoprim and 400 mg of sulfamethoxazole, so for an average-sized adult, the dose is 3 ampules every 6 hours. Potential side effects include rash (occurring in approximately 50% of patients with AIDS), neutropenia, and anemia. If side effects are mild (including a mild rash), treatment can usually be continued. For less-severe rashes, diphenhydramine may provide relief.⁸⁸

For patients who cannot tolerate TMP-SMX, intravenous (not aerosolized) pentamidine (4 mg/kg once daily) is regarded as the second choice.^{89,90} Because pentamidine may cause hypotension during infusion, it should be given over the course of an hour, and blood glucose levels should be monitored, since pentamidine can cause hypoglycemia.^{xix} Because this drug is not active against bacteria, appropriate coverage for community-acquired pneumonia should be added until PCP is verified. Some experts prefer clindamycin 600 mg IV (or 900 mg IV for severe disease) every 8 hours, plus pri-

maquine 15 mg PO each day as a second-line agent because it is less toxic than pentamidine. Other alternative treatment regimens for PCP include trimethoprim plus dapsone, trimetrexate plus leucovorin, and atovaquone. Among the second-line choices, the combination of clindamycin and primaquine may be more effective than IV pentamidine in the treatment of TMP-SMX-resistant infections.^{xvi,xvii} However, no prospective clinical trials have evaluated the optimal approach to patients who have not responded to TMP-SMX.

Additional Antibiotics For HIV-Infected Patients With Respiratory Complaints

In addition to *P jiroveci*, other typical pathogens, especially *S pneumoniae*, can cause pneumonia in patients with AIDS. Because TMP-SMX is active against the most common bacterial pathogens, some ED clinicians had previously used it as the sole agent for AIDS patients with pneumonia of mild-to-moderate severity. However, because of increasing resistance to TMP-SMX among strains of *S pneumoniae* (18% of all strains in 2008^{xviii}) many physicians add a second drug, such as a third-generation cephalosporin or a quinolone, for patients with moderate-to-severe pneumonia.

There is insufficient evidence to support coverage for “atypical organisms” in patients with HIV-related infections. However, in 1 recent study of community-acquired pneumonia, *P jiroveci*, *M tuberculosis*, *S pneumoniae*, and *M pneumoniae* were the most common etiologic agents in HIV-positive patients.⁹² A macrolide or a third-generation quinolone would have been a useful addition in this population. The addition of an antibiotic with antipseudomonal activity may be valuable in those with advanced immunosuppression, since *Pseudomonas pneumoniae* occurs in those with end-stage disease.

Although it is important for the ED clinician to consider a diagnosis of TB so that respiratory isolation precautions can be followed, it is usually not critical to begin treatment, although empirical treatment should be considered when the findings on chest x-ray strongly suggest TB (ie, apical infiltrates with adenopathy). Typically, TB is treated with the same drugs whether the patient is infected with HIV or not. However, rifabutin is often substituted for rifampin to avoid drug interactions in patients taking protease inhibitors.⁹³

Steroids For HIV-Infected Patients With Respiratory Complaints

Steroids should be used as adjunctive therapy for those with more severe PCP. Prednisone will reduce the incidence of respiratory failure and mortality in an important subgroup of patients — those with a PaO₂ less than 70 mm Hg or an A-a gradient above 35 mm Hg.⁹⁴

When indicated, prednisone should be started at a dose of 40 mg orally twice a day, with the first dose given 15 to 30 minutes before the antibiotic and the dosage tapered over a 21-day course of therapy. If the patient is later shown to have bacterial pneumonia or TB, the steroids can be stopped without causing any serious adverse consequences.

A recent Cochrane Review of studies carried out over the course of 24 years (1980–2004) found 6 studies that compared corticosteroid treatment to placebo or usual care in HIV-seropositive patients with PCP in addition to baseline treatment with trimethoprim-sulfamethoxazole, pentamidine, or dapsone-trimethoprim. The endpoint was mortality, and patients were excluded if they had no or only mild hypoxemia. The review supports the guidelines in confirming that prednisone is beneficial in patients with substantial hypoxemia.^{xix}

Central Nervous System Complaints In HIV-Infected Patients

Etiology Of Central Nervous System Complaints In HIV-Infected Patients

After the lung, the CNS is the next most common site of serious infections in HIV-infected persons who present to the ED. In the early 1990s, it was estimated that 40% to 70% of HIV patients will develop a symptomatic neurologic disorder over the course of their lifetime.⁹⁵ Toxoplasmosis is the most common CNS infection, occurring in approximately 3% to 10% of United States AIDS patients.^{54,96} Immigrants from Africa, Latin America, and Haiti are 3 to 4 times more likely to develop CNS toxoplasmosis than American-born patients with AIDS.⁹⁷ A recent study puts the prevalence of neurologic and psychiatric conditions to be 10% to 20% in western countries.^{xx}

Cryptococcal meningitis is also very common, developing in up to 10% of patients.⁵⁵ Others with AIDS may suffer from TB of the CNS, lymphoma, or fungal infections with organisms such as *C immitis* and *H capsulatum*. Viral infections usually involve cytomegalovirus and herpes simplex virus. Additional CNS diseases include progressive multifocal leukoencephalopathy and syphilis. HIV itself can produce a progressive dementia with brain atrophy.⁹⁸ Patients demonstrate cognitive abnormalities affecting attention, memory, and information processing.⁹⁹

Drug toxicity should also be considered in the differential diagnosis of altered mental status in patients with AIDS. Many antiretrovirals and other antimicrobials are associated with altered mental status, weakness, or other neurologic complaints. Efavirenz, in particular, is associated with dizziness and confusion.

History And Physical Examination For Central Nervous System Complaints In HIV-Infected Patients

Although fulminant presentations of meningitis occur, many CNS infections in HIV-infected patients are indolent, and the presenting symptoms and signs may be subtle.

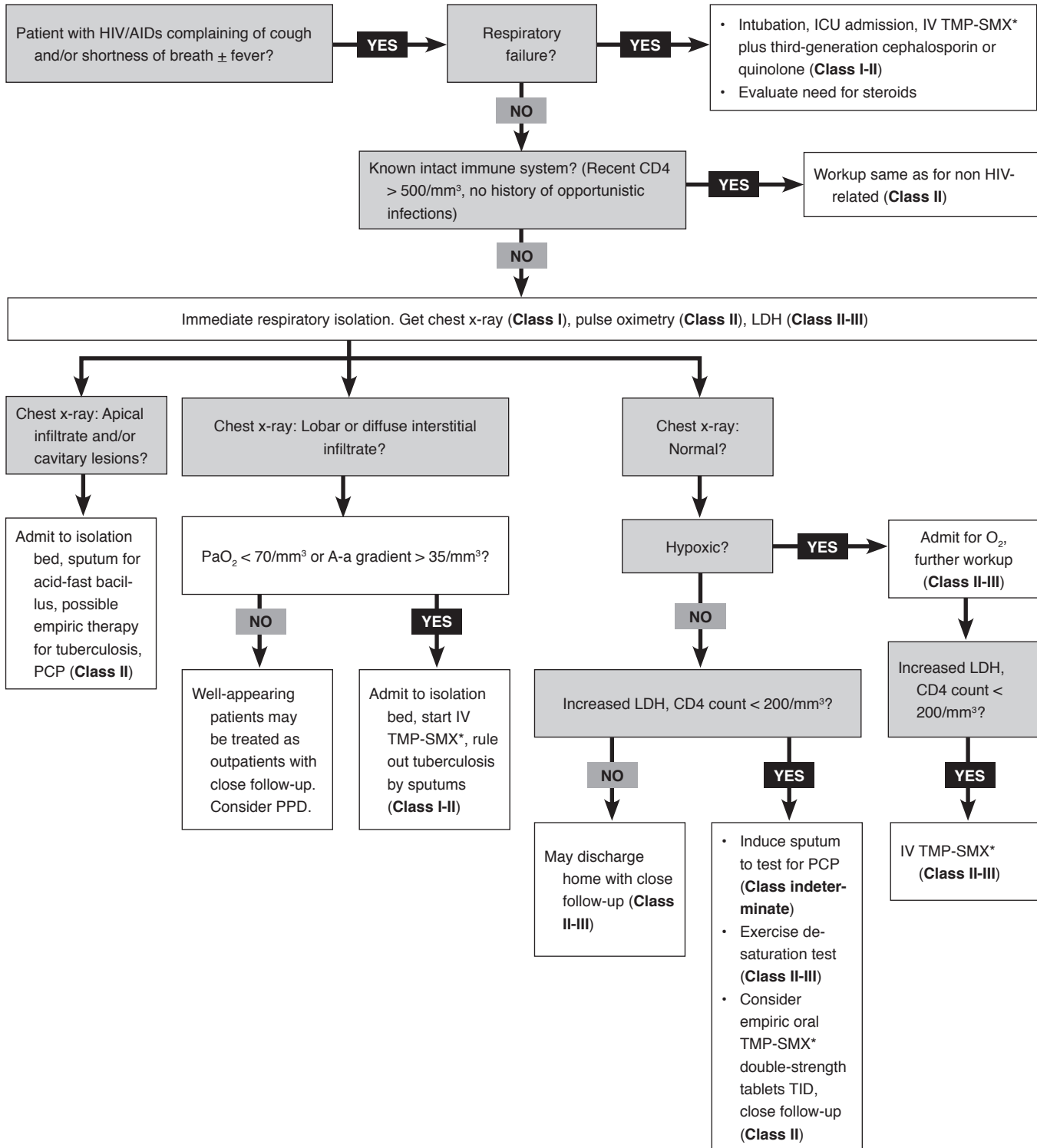
Fever and headache are often the only presenting symptoms in AIDS patients with CNS toxoplasmosis, with each occurring in about half the cases. It is not uncommon for the neurologic examination to be normal in AIDS-related toxoplasmosis despite the sometimes dramatic mass lesions seen on CT scanning of the head. Altered mental status is found in only about 60% of patients, seizures in about 30%, and focal deficits in about 60%.¹⁰⁰

As with toxoplasmosis, cryptococcal meningitis may present with only fever and nonspecific constitutional symptoms such as nausea and malaise. Nuchal rigidity and other meningeal signs are often absent. Cryptococcal meningitis is associated with a headache in the vast majority of patients (75%-90%).^{101,102} Other findings include vomiting (42%), altered mentation (28%), stiff neck (22%), photophobia (18%), focal deficits (6%), and seizures (4%). Unlike bacterial meningitis, cryptococcal meningitis tends to develop slowly, and the patient's complaints may be relatively mild.¹⁰³

Another important CNS infection to consider in patients with AIDS is CMV retinitis. This presents as a painless loss of vision, usually in patients with end-stage disease.¹⁰¹ The characteristic retinal lesions have a central pallor with surrounding hemorrhage, the fundus being imaginatively referred to as a "cheese-and-tomato pizza." Lesions usually develop at the periphery (causing lateral field vision loss) and progress inward toward the macula, eventually resulting in blindness in some cases. In early retinitis, patients may complain of floaters or blind spots, and the lesions may be difficult to identify on funduscopic examination. Therefore, even when the retina appears normal on funduscopic examination, any HIV-positive patient with complaints suggestive of CMV retinitis should be referred to an ophthalmologist within 1 to 2 days.

Many patients with advanced AIDS who respond to HAART may experience stabilization of or improvement in their neuropsychologic function, but they never quite achieve parity, even years after the initiation of HAART and subsequent immune recovery (based on CD4 lymphocyte counts).^{xxi} Because some of these patients may not be ideal historians, it is important for the ED clinician to tease out the chronicity of any neurologic/psychiatric findings.

Clinical Pathway For Evaluation Of Respiratory Complaints In HIV/AIDS Patients



For Class Of Evidence Definitions, see page 1.

*Trimethoprim-sulfamethoxazole: 15 mg/kg of trimethoprim in 4 divided doses. If sulfa allergy: Use IV pentamidine plus third-generation or quinolone.

Note: Since chest x-ray findings are unreliable in patients with advanced HIV infection, essentially any finding — including a “normal” pulmonary pattern — may be seen with PCP or TB. These diseases must be addressed in every patient with AIDS and respiratory complaints. (Class II)

Diagnostic Testing For Central Nervous System Complaints In HIV-Infected Patients

Imaging Tests For Central Nervous System

Complaints In HIV-Infected Patients

A CT scan of the head should be obtained for patients with AIDS who have any new CNS-related symptoms, including headache. In a study of 110 HIV-infected patients, researchers looked for neurologic signs or symptoms that would predict new focal lesions on head CT in HIV-infected patients.¹⁰⁴ The presence of any 1 of the following variables was 100% sensitive for a new focal lesion and would have resulted in a 37% reduction in the number of head CTs ordered in the ED:

- new seizure
- depressed or altered orientation
- headache, unusual in quality
- prolonged headache (≥ 3 days)

Another retrospective study looked at HIV-infected patients who complained of headache to identify those at low risk for an intracranial mass lesion.¹⁰⁵ Patients without focal neurologic signs, altered mental status, seizure, or decreased CD4 lymphocytes were not likely to have intracranial mass lesions. Other reviews confirm that a low CD4 count ($\leq 200/\text{mm}^3$) is an important risk factor for a positive CT scan in HIV-positive patients who present with uncomplicated headache (ie, no altered mental status, meningeal signs, neurologic findings, or symptoms of subarachnoid hemorrhage).¹⁰⁶ In this report, the authors also suggest that patients with uncomplicated headaches (excluding those with altered mental status, meningeal signs, neurologic findings, or complaints of “the worst headaches of my life”) along with CD4 counts greater than $200/\text{mm}^3$ should be managed without requisite CTs. If a lesion is strongly suspected, magnetic resonance imaging (MRI) is recommended.

Although some hospitals routinely use contrast in the CT evaluation of an HIV-infected patient with headache or neurologic symptoms, others rely on non-contrast scans. In 1 study, for every positive enhanced scan in an HIV-infected patient, the unenhanced scan was abnormal, suggesting that intravenous contrast may be unnecessary in the ED setting.¹⁰⁷ Typically, the CT scan shows multiple lesions (which will enhance if contrast is given). Magnetic resonance imaging is slightly more sensitive than CT scanning and may be indicated in patients strongly suspected of having toxoplasmosis despite a nondiagnostic CT.

Approximately 20% of patients with toxoplasmosis will have a single lesion.¹⁰⁸ Although other etiologies such as lymphoma should be considered when a solitary lesion is found, it is common practice to treat these patients empirically for toxoplasmosis and consider biopsy later if they fail to respond to treatment. Toxoplasma antibody titers are

usually unavailable within the time frame of an ED evaluation but, more importantly, are insensitive to CNS toxoplasmosis.¹⁰⁹

Recent studies have not provided definitive guidance regarding the initial neuroimaging modality. The most recent CDC guidelines (2009) suggest that CT and/or MRI is a useful tool in the diagnosis and treatment of intracranial processes in HIV-seropositive patients.^{xxii}

After neuroimaging has ruled out intracranial mass lesions, LP is indicated for immunosuppressed patients with any acute CNS-related symptoms. (See the Clinical Pathway For Evaluation Of CNS Complaints In HIV/AIDS Patients, page 71.) The ED clinician should perform LP in patients with CD4 counts below $200/\text{mm}^3$ who do not appear toxic but complain of headache or altered mental status.

Lumbar Puncture For Central Nervous System Complaints In HIV-Infected Patients

When performing the LP, measure the opening pressure when feasible. An elevated opening pressure is a common finding in cryptococcal meningitis, occurring in about 70% of cases. Cerebrospinal fluid (CSF) should be sent for cell count (including differential), protein, glucose, India ink stain, and CSF cryptococcal antigen. In addition to routine bacterial cultures, fungal and mycobacterial cultures should also be performed. Because of the higher incidence of neurosyphilis in HIV-infected people, order a CSF VDRL even in patients without neurologic symptoms consistent with syphilis. In a recently published retrospective study, 202 of 231 with concurrent HIV infection and syphilis were asymptomatic neurologically at the time of their lumbar puncture.^{xxiii}

In AIDS-related cryptococcal meningitis, the CSF may appear normal or nearly normal on standard studies; glucose is less than 40 mg/dL in only 24%, protein is greater than 45 mg/dL in only 55%, the WBC count exceeds $20/\text{mm}^3$ in only 21%, and the polymorphonuclear cell count is above 10% in only 16%.¹⁰¹

India ink stains reveal the fungus in approximately three-fourths of patients, but a CSF cryptococcal antigen test has over 90% sensitivity and may be the only indication of cryptococcal meningitis. The serum cryptococcal antigen test is less sensitive than the CSF cryptococcal antigen test for the diagnosis of meningitis.¹⁰¹

Treatment Of Central Nervous System Complaints In HIV-Infected Patients

Most CNS infections in HIV-infected persons follow an indolent course, and treatment can await a diagnosis based on CT scan and LP results. If a patient presents with a fulminant illness suggestive of acute bacterial meningitis, treat empirically before sending the patient for CT scanning.

Patients with presumed toxoplasmosis should

be admitted and treated with pyrimethamine and sulfadiazine, or pyrimethamine and clindamycin for those with sulfa allergies and as a second-line agent.¹¹⁰ Leucovorin should be given as an adjuvant agent to prevent hematologic toxicities.^{xxiv} A recent study (albeit with only 77 subjects) suggests that TMP-SMX may also be an effective therapy and better-tolerated by patients. ED clinicians may consider TMP-SMX, especially for patients who cannot tolerate an oral therapy.^{xxv}

Because this infection usually progresses slowly, it is not critical to start therapy immediately in the ED. Steroids should be given if significant surrounding edema is found.¹¹⁰ Because toxoplasmosis in patients with AIDS cannot be cured, lifelong secondary prophylaxis is required.

Therapy for cryptococcal meningitis is usually initiated with IV amphotericin B on an inpatient basis combined with flucytosine.¹¹¹ Flucytosine has been found to improve clearance of cryptococci from the CSF. ED clinicians should be cognizant of possible renal dysfunction, since flucytosine is cleared through the kidneys.^{xxvi} Complications such as headache, nausea, and vomiting may be reduced by removing CSF from patients with an elevated opening pressure.¹¹⁴ If symptoms are minimal and CSF parameters are acceptable (ie, WBC < 20/mm³, cryptococcal antigen < 1:1024), some ED clinicians opt for outpatient management with oral fluconazole.¹¹⁵ However, oral fluconazole with flucytosine is an inferior therapy and should be second-line choice. The combination of fluconazole/flucytosine is better than amphotericin B alone, so this combination may be considered in patients who are unable to tolerate treatment or experience treatment failure.^{xxvii} Close follow-up and consultation with the primary care physician are essential if outpatient management is recommended.¹¹²⁻¹¹⁵

Patients with normal CSF chemistries and a negative India ink stain who do not appear toxic and have a normal mental status can be sent home if follow-up can be arranged. Should the cryptococcal antigen test come back positive, a delay of a few days should not have a serious impact on outcome.

Like PCP and toxoplasmosis, cryptococcosis frequently recurs and thus requires secondary prophylaxis with fluconazole. If an immunosuppressed AIDS patient with a history of cryptococcal meningitis stops taking fluconazole, it is highly likely that he or she will relapse.¹¹⁶

Patients with retinal lesions characteristic of CMV retinitis should be admitted to the hospital for a 2- to 3-week course of therapy with IV ganciclovir or foscarnet. Oral val-ganciclovir recently became available for induction therapy. Cidofovir is another antiviral drug that is used in some cases. These therapies have similar efficacies but different resistance patterns and side effect profiles.¹¹⁷ Lifelong maintenance therapy is usually required to prevent

relapses, but it can be stopped if the immune system is reconstituted with HAART. Some patients can be controlled with oral ganciclovir maintenance or ganciclovir ocular implants, but those with aggressive disease may require IV maintenance therapy through a central catheter.¹¹⁸

"The AIDS epidemic has rolled back a big rotting log and revealed all the squirming life underneath it, since it involves, all at once, the main themes of our existence: sex, death, power, money, love, hate, disease, and panic. No American phenomenon has been so compelling since the Vietnam War."

— Edmund White, *AIDS: An American Epidemic*

Abdominal Complaints In HIV-Infected Patients

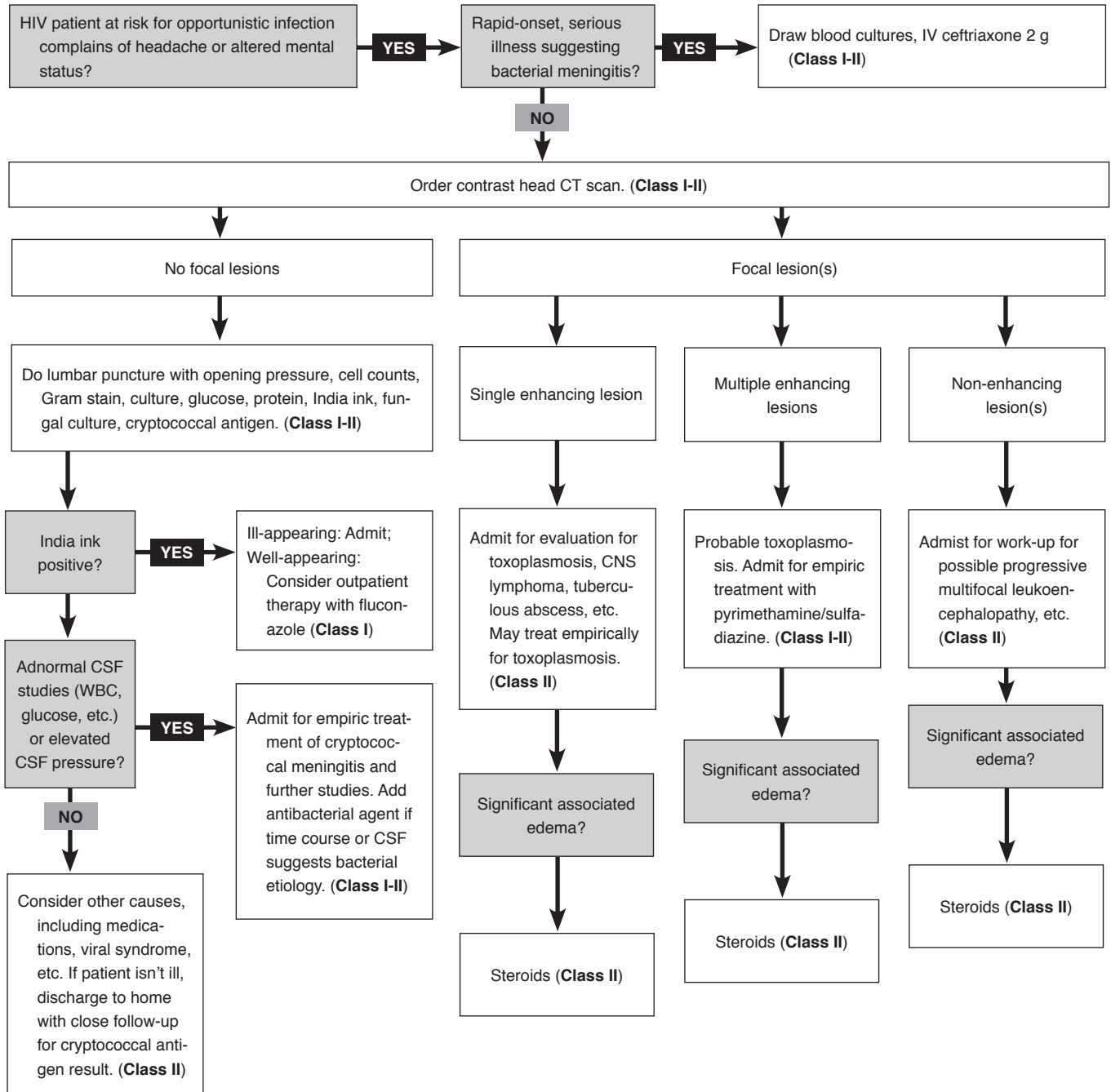
In addition to respiratory and neurologic problems, abdominal complaints (diarrhea and dysphagia being the most common) often prompt AIDS patients to seek immediate care.

Patients with esophagitis usually complain of pain and difficulty swallowing. *Candida albicans* is most often responsible for esophagitis in AIDS (about 60% to 75% of cases).¹¹⁹ Other etiologies include CMV and herpes simplex virus. The anti-retroviral drug ddC can produce esophageal ulcers, and some patients with HIV infection have idiopathic esophageal ulcers that respond to steroids.¹²⁰ Those using topical solutions for oral candidiasis, such as clotrimazole troches or nystatin suspensions, may not have visible evidence of oral or pharyngeal thrush but still have esophageal disease; topical solutions are effective for oral candidiasis but not for esophageal infection.

Abdominal pain in AIDS patients can be due to a wide variety of etiologies, including CMV colitis, lymphoma, appendicitis, MAC infection, pancreatitis, and AIDS cholangiopathy.¹²¹⁻¹²³ AIDS cholangiopathy typically presents with right upper quadrant pain and fever in patients with advanced AIDS (CD4 < 50/mm³). Because of shared routes of transmission, hepatitis B and C frequently complicate HIV infection.¹²⁴ Remember that some abdominal culprits may be unrelated to the immune suppression, such as peptic ulcer disease, hernias, gastroenteritis, ectopic pregnancy, and the like. Opportunistic infections can cause perforation and obstruction. CMV of the gastrointestinal tract may lead to fecal peritonitis.¹²² In addition to the myriad opportunistic entities, the gastrointestinal mucosal immune system itself is under attack in patients who are HIV-seropositive.^{xxviii} The effects of this are still being studied.

Diarrhea is often a debilitating problem for AIDS patients; nearly all have it at some point during their illness. AIDS-related diarrhea is difficult to treat. The cause is often obscure, and even when pathogens are identified, they may be resistant to therapy.¹²⁵

Clinical Pathway For Evaluation Of Central Nervous System Complaints In HIV/AIDS Patients



For Class Of Evidence Definitions, see page 1.

Bacterial pathogens such as *Salmonella*, *Shigella*, and *Campylobacter* can lead to acute-onset diarrhea. AIDS patients are at particular risk for recurrent *Salmonella* bacteremia.¹²⁶ Indolent, chronic diarrhea is more likely the result of parasitic, mycobacterial, or viral infection (including *Giardia lamblia*, *Cryptosporidium parvum*, and *Isospora belli*); CMV infection; and MAC. In late-stage AIDS, CMV and MAC frequently cause chronic diarrhea that is resistant to treatment. CMV colitis develops in approximately 8% to 16% of patients with advanced AIDS, resulting in chronic diarrhea.¹²⁷

"From this moment on, our response to AIDS must be no less comprehensive, no less relentless and no less swift than the pandemic itself. I was a soldier and I know of no enemy in war more insidious or vicious than AIDS, an enemy that poses a clear and present danger to the world."

— Colin Powell, former US Secretary of State

History And Physical Examination For HIV-Infected Patients With Abdominal Complaints

Obtaining a medication history is important in patients who present with abdominal pain. Pancreatitis occurs in up to 10% of patients taking ddI, and it is also associated with ddC, 3TC, TMP-SMX, pentamidine, and others agents. Indinavir can cause kidney stones in about 10% of cases. The ED clinician should also ask about recent antibiotic use. Because AIDS patients are frequently on prolonged courses of antibiotics, diarrhea due to *C difficile* is common and can present as a fulminant illness.¹²⁸ In addition to the routine questions regarding the history of present illness, consider the sexuality of those who present with acute diarrhea. Persons practicing receptive anal intercourse are at increased risk of proctocolitis due to sexually transmitted organisms such as gonorrhea, chlamydia, herpes, or syphilis.

Laboratory Studies For HIV-Infected Patients With Abdominal Complaints

In the evaluation of abdominal pain in patients with HIV infection, the usefulness of laboratory studies varies between patients and tests. While some consider a CBC obligatory, it is wise to remember that HIV-infected patients with surgical disease may have a normal or low WBC count. In 1 small study, 6 of the 9 HIV-positive patients with appendicitis did not have an elevated WBC count.¹²⁹

A serum lipase and/or amylase level may be especially useful to look for drug-induced pancreatitis in patients taking antiretroviral therapy. Because ddI causes pancreatitis in up to 10% of patients, serum amylase and lipase should be measured when a patient on ddI presents with vomiting and epigastric pain. The value of routine liver function tests

remains unknown, but these tests may be indicated for those with jaundice or right upper quadrant pain. A markedly elevated alkaline phosphatase is characteristic of AIDS cholangiopathy.

Many patients who present with recurrent or chronic diarrhea have already had multiple outpatient stool studies in an attempt to identify a pathogen. It is not necessary to repeat studies on a patient with chronic diarrhea, but those with newly developed diarrhea or a significant change in the pattern of diarrhea merit evaluation. Stool cultures may identify potentially treatable bacterial pathogens. *Giardiasis* is identified by stool ova and parasite examinations, while a modified acid-fast stain can detect *Cryptosporidium* and *Isospora*.

Imaging Studies For HIV-Infected Patients With Abdominal Complaints

Laparotomy is unnecessary in most AIDS patients with abdominal pain.¹³⁰ In 1 small study of HIV-infected patients with appendicitis, only one-third of AIDS patients with right-lower-quadrant pain had appendicitis, whereas more than 90% of HIV-positive patients without AIDS had the disease.¹³¹ Rational use of the abdominal CT scan can help avoid unwarranted surgery in the patient with AIDS.¹³² A noncontrast helical CT is useful in the patient with flank pain and fever, especially in those on medications that predispose to renal stones, such as indinavir. Ultrasound may also be useful in those with right-upper-quadrant pain. In AIDS cholangiopathy, ultrasound reveals dilatation of intra- and extrahepatic bile ducts with wall thickening.¹³³ Papillary stenosis is narrowing of the duodenal papilla, where the common bile duct enters the duodenum. It occurs in about half the patients with AIDS cholangiopathy, and stones are typically absent.

Pelvic ultrasound is recommended in women with AIDS and pelvic inflammatory disease since they tend to have a very high incidence of tubo-ovarian abscess.¹³⁴ Tubo-ovarian abscesses may occur in up to one-third of HIV-positive women with salpingitis.¹³⁵

Endoscopy For HIV-Infected Patients With Abdominal Complaints

Because *C albicans* infection is such a common cause of esophagitis, empiric therapy is preferable to testing as an initial strategy.¹³⁶ Follow-up must be arranged so that patients who worsen or fail to improve within 7 to 10 days can undergo further testing (including esophagoscopy) to rule out herpes esophagitis or infection with CMV or resistant fungi. In patients with cholangitis, endoscopic retrograde cholangiopancreatography is usually done to visualize the biliary tree. The gastroenterologist can collect specimens for culture and staining as well as perform therapeutic papillotomy if stenosis is found. Colonoscopy is occasionally employed in cases of

refractory diarrhea. CMV colitis is suggested by erythematous, friable mucosa, and the diagnosis can be verified by biopsy.

Treatment Of HIV-Infected Patients With Abdominal Complaints

Oral and esophageal candidal infections can be treated with fluconazole 200 mg on day 1 and then

100 mg daily.¹³⁷ Patients with oral infection alone require 2 weeks of therapy, whereas those with esophagitis require 3 weeks of therapy (or therapy that lasts 2 weeks longer than the symptoms do).¹³⁸ Some patients with severe or resistant esophageal candidiasis may require hospital admission for amphotericin B therapy.¹³⁹ Herpes esophagitis is treated with acyclovir.

Cost-Effective Strategies For Patients With HIV/AIDS

1. Base the intensity of the work-up on the degree of immunosuppression.

If a patient has a normal or near-normal CD4 count, he or she might not need a chest film for a simple cough or a CT scan/ LP for a routine headache. Searching the laboratory computer for a recent CD4 count may prevent wasting time and money in fruitless investigations. An absolute lymphocyte count above 2000/mm³ suggests that the CD4 count is above 200/mm³. HIV-positive patients with a CD4 count of 500/mm³ or more are not at risk for opportunistic infections. Those with a CD4 count between 200/mm³ and 500/mm³ may be slightly more susceptible to tuberculosis and oral thrush but not PCP, Cryptococcus, toxoplasmosis, or disseminated MAC. If the patient has a recent CD4 count above the "dangerous range," medical evaluation can proceed without special concern for unusual organisms.

Risk Management Caveat: Many patients do not know their CD4 count. Others may have had a low or normal count several months ago, which may have dipped below 200/mm³ in the ensuing time interval. When in doubt, assume the patient is at risk for opportunistic infections.

2. Consider outpatient therapy for well-appearing patients with PCP.

Not every patient with PCP requires hospitalization. Patients at low risk for complications who appear well and are not hypoxic may be discharged on appropriate oral medication.

Risk Management Caveat: Patients who are discharged must have reassuring chest films and an acceptable oxygenation reading. They should be reliable, demonstrate that they can tolerate fluids, and have early follow-up arranged.

3. Limit laboratory testing for PCP.

In some hospitals, the diagnosis of PCP is made only after demonstration of the organism on

induced sputum or bronchiolar lavage. In other centers, a clinical picture alone is adequate to initiate therapy. In 1 cost analysis, the use of exercise saturation measurements (using a desaturation of 3 points during exercise) was 1 of the most sensitive and economical approaches to the diagnosis of PCP.¹⁵⁹ The addition of an LDH measurement may be helpful.

Risk Management Caveat: Patients who appear acutely ill or toxic, those with atypical presentations, and individuals with unusual findings on chest radiography may require more extensive microbiologic investigations. Be liberal in applying a PPD to HIV-infected patients with pulmonary complaints, especially if they are not admitted to the hospital. (Of course, do not order a PPD if they have had a history of TB.)

4. Limit the LP/CT pathway to patients who are likely to have CNS disease.

A low CD4 count in association with a new or different headache is a worrisome finding. One study showed that HIV-infected patients were at low risk for a mass lesion if they had no focal neurologic signs or alteration of mental status, no history of seizures, and a CD4 + cell count of 200/mm³ or higher (or a total lymphocyte count above 2000/mm³ if CD4 + cell counts were not available).¹⁰⁵ Another study¹⁶⁰ showed that no case of an opportunistic meningitis occurred in a patient with a CD4 count greater than 200/mm³.

Risk Management Caveat: Certain presentations mandate the CT/LP pathway. These include focal neurological findings, altered mental status without an obvious cause (such as hypoglycemia), and new-onset seizures. If the patient complains of a new headache and the CD4 count is below 200/mm³ or unknown, CT followed by LP is indicated. Any patient who appears toxic without a source or who has meningeal signs needs a CT and LP regardless of the CD4 count.

While the care of specific intra-abdominal conditions is beyond the scope of this chapter, the ED clinician must recognize certain life threats. Pancreatitis in the AIDS patient is especially dangerous. In 1 recent review, nearly one-third of AIDS patients hospitalized with pancreatitis died.¹⁴⁰ Standard scoring systems (such as Ranson's and Imrie's criteria and the APACHE II scoring system) failed to predict the severity of the disease. Even "routine" conditions become more ominous in the compromised host and call for heightened vigilance. AIDS patients with appendicitis have a perforation rate of up to 40%.¹⁴¹

If bacterial infection is strongly suspected because of acute severe diarrhea with fever, empiric treatment with an antibiotic such as ciprofloxacin (500 mg PO twice daily for 3-5 days) would be appropriate. Quinolones are active against the most common bacterial pathogens, such as *Salmonella*, *Shigella*, and *Campylobacter*. Treatment for parasitic infection is often ineffective; no uniformly effective anticyptosporidial therapy is available, although some patients respond to paromomycin plus azithromycin.¹⁴² TMP-SMX is usually effective for treating isosporiasis, although continued suppressive therapy may be required owing to the high incidence of recurrence.¹⁴³ Symptomatic treatment with diphenoxylate or loperamide may be the most reasonable way to manage AIDS-related diarrhea, especially in late-stage disease with chronic diarrhea.

Small case studies suggest that ganciclovir may treat CMV colitis in patients without overt immunocompromise.^{xxviii} Ganciclovir does appear to treat CMV esophagitis in AIDS.^{xxix} Most patients will improve after treatment, but relapse is common.¹⁴⁴ Researchers suggest that relapse is common simply because of the severity of the immunocompromise in these patients. Definitive treatment may actually be improvement of patients' immune functions, as evidenced by the decrease in CMV colitis after the introduction of protease inhibitors in the mid-1990's as part of the HAART regimen.^{xxx}

Antimicrobial Therapy In The Management Of HIV Infections

The antimicrobial therapy for HIV infections falls into 2 categories: the prophylaxis and treatment of opportunistic infections and the direct suppression of HIV replication. An ED clinician should be able to recognize the common medications used and their customary toxicities. (See Table 3.) PCP prophylaxis is now the standard of care for a patient with a CD4 count below 200/mm³. It is also used in certain high-risk patients, such as those newly diagnosed with an AIDS-defining illness.^{145,146} TMP-SMX is most commonly prescribed, but some

patients, because of allergy, may take alternative therapies such as dapson, aerosolized pentamidine, clindamycin plus primaquine, or atovaquone, but these alternative therapies are generally less effective than is TMP-SMX.¹⁴⁷ Azithromycin (1200 mg weekly) or rifabutin (300 mg daily) are prescribed as prophylaxis against MAC for patients with a CD4 count less than 50/mm³.¹⁴⁶ The ED clinician must recognize that no prophylaxis regimen is 100% effective, and infection can occur despite faithful adherence.

Although ED clinicians are not expected to manage antiretroviral therapy in AIDS patients, they should be familiar with the basic principles of anti-

Table 3. Common Adverse Reactions To Drugs Used In HIV-Infected Patients

3TC:	Anemia, headache, nausea, diarrhea
AZT:	Anemia, leukopenia, nausea, fatigue, nail pigmentation, myositis
d4T:	Peripheral neuropathy, anemia, leukopenia
ddC:	Peripheral neuropathy, rash, pancreatitis,* oral ulcers, hepatitis, neutropenia
ddl:	Pancreatitis,* peripheral neuropathy, hypocalcemia, hypokalemia, diarrhea, hepatitis, arrhythmias
Abacavir:	Hypersensitivity reaction (fever, rash), headache, gastrointestinal upset
Amprenavir:	Rash, nausea, diarrhea, paresthesias, depression, hyperglycemia
Atovaquone:	Headache, diarrhea, nausea, rash, fever
Cidofovir:	Renal toxicity common, gastrointestinal upset, neutropenia
Dapsone:	Hemolytic anemia,* rash, methemoglobinemia, headache, nephrotic syndrome
Delavirdine:	Rash common, headache, gastrointestinal upset, abnormal liver function tests
Efavirenz:	Dizziness, insomnia, rash, hepatitis
Fluconazole:	Drug interactions common (eg, warfarin, phenytoin), nausea, abnormal liver function tests
Foscarnet:	Renal insufficiency, electrolyte abnormalities, headache, tremors
Ganciclovir:	Bone marrow suppression, increased liver function tests
Indinavir:	Nausea, kidney stones,* abnormal liver function tests
Lopinavir/Ritonavir:	Nausea, diarrhea, abnormal liver function tests, drug interactions common
Nelfinavir:	Diarrhea, abnormal liver function tests
Nevirapine:	Rash common and may be severe, gastrointestinal upset, abnormal liver function tests
Pentamidine:	Hypotension,* hypoglycemia,* hyperglycemia, hyperkalemia, arrhythmias, renal insufficiency
Pyrimethamine:	Anemia, leukopenia, thrombocytopenia (requires folic acid), nausea, seizures
Rifabutin:	Fever, nausea, rash, abdominal pain, uveitis
Ritonavir:	Nausea, diarrhea, abnormal liver function tests, drug interactions common
Saquinavir:	Diarrhea, nausea, abdominal pain
TMP-SMX:	Rash, fever, neutropenia, anemia, nausea, hepatitis, photosensitivity
Trimetrexate:	Anemia, leukopenia, thrombocytopenia (requires folic acid), nausea, renal insufficiency, hepatitis

* Indicates most significant causes

retroviral therapy and the drugs used.¹⁴⁸ Initiating antiretroviral therapy for new HIV infections is best left to the specialist. Changes to a patient's regimen by an ED clinician should only extend to stopping medications in the event of an adverse reaction.

Antiretroviral drugs are typically given in combination. Most commonly, 2 nucleoside analogs are combined with a protease inhibitor. (See Table 4.) A non-nucleoside reverse transcriptase inhibitor is sometimes used in place of a protease inhibitor. The viral load is measured periodically to determine response. If the viral load increases or fails to decline, the drug regimen is changed. Unfortunately, many patients find it difficult to comply with complicated and often toxic antiretroviral regimens. For example, in 1 large cohort over 1 year, 29% of patients with HIV infection had their regimens modified because of toxicity, and 26% stopped the medications altogether.¹⁴⁹

At any given time, the patient with AIDS is likely to be taking many powerful medications; 8 to 10 drugs taken concurrently is not uncommon. Almost every drug used for HIV infection can cause headache, malaise, nausea, abdominal discomfort, and diarrhea, and many have severe toxicity that may result in an ED visit. (See Table 3.) Drug interactions are common.¹⁵⁰

*"AIDS obliges people to think of sex as having, possibly, the direst consequences: suicide. Or murder."
— Susan Sontag, AIDS and Its Metaphors*

Postexposure Prophylaxis For HIV

Depending on the circumstances, sticking oneself with a needle can be a profoundly disturbing event. Based on a number of assumptions, the cumulative risk of contracting HIV infection over a 30-year ED career may be as high as 1.4%.¹⁵¹

In prospective studies, the average risk of HIV transmission after a single percutaneous exposure to HIV-infected blood is approximately 0.3% (95% confidence interval [CI], 0.2%-0.5%)¹⁵²; after a mucous membrane exposure, this risk is approximately 0.09% (95% CI, 0.006%-0.500%).¹⁵³ The risk of transmission appears to depend on the amount of infected fluid to which the person is exposed and the amount of HIV in that fluid.¹⁵⁴

Case-control studies demonstrate that postexposure prophylaxis with antiretroviral drugs may reduce the likelihood of seroconversion.^{154,155} (See Table 5, page 77.) Because of the toxicity associated with these medications, the ED clinician should provide adequate information to the patient so he or she can make an informed choice regarding postexposure prophylaxis.

Occasionally, patients may request HIV prophylaxis after sexual assault or after unprotected

consensual sex. The risk associated with a specific sexual encounter cannot accurately be determined, but available data allow an estimate of the range of risk for various types of exposures.^{156,157} The risk appears to be highest with unprotected receptive anal intercourse (0.008 to 0.032 per episode) — higher than the risk from occupational needlesticks. The risk from vaginal intercourse is higher for male-to-female transmission (0.0005 to 0.0015) than from female-to-male (0.0003 to 0.0009). Although the risk from oral-genital contact has not been reported, it appears to be low.

Although there is no direct evidence that postexposure treatment will prevent HIV infection after sexual exposure, it is reasonable to believe that the risk can be reduced, given the data regarding occupational and perinatal exposures.¹⁵⁸ The decision to provide HIV prophylaxis after sexual contact involves an assessment of the risk of transmission, the potential benefit of prophylaxis, and the cost and toxicity of antiretroviral drugs. For most sexual exposures, the patient should be informed of the risks and benefits of postexposure prophylaxis but advised that the risk of infection is low and is likely outweighed by the cost and toxicity of postexposure prophylaxis. If postexposure prophylaxis is given, a 2-drug regimen for 4 weeks would be appropriate for most, with 3-drug regimens reserved for only the highest risk exposures (eg, receptive anal intercourse with a person known to be infected with HIV).

For healthcare workers, HAART PEP should be instituted if they are evaluated within 36 hours

Table 4. Antiretroviral Drugs

Nucleoside analogs

- Zidovudine (AZT, ZDV)
- Didanosine (ddI)
- Zalcitabine (ddC)
- Stavudine (D4T)
- Lamivudine (3TC)
- Abacavir (ABC)

Non-nucleoside reverse transcriptase inhibitors

- Nevirapine
- Delavirdine
- Efavirenz

Protease inhibitors

- Saquinavir
- Ritonavir
- Indinavir
- Nelfinavir
- Amprenavir
- Lopinavir/Ritonavir

Nucleotide reverse transcriptase inhibitor

- Tenofovir

of exposure. In vivo evidence from a small study of healthcare workers who were exposed percutaneously to HIV but who did not seroconvert suggests that limited viral replication may occur without establishment of infection. Therefore, if limited replication following exposure is a frequent event, it is even more important for HAART to be initiated early to contain viral proliferation and allow cytotoxic T cells to kill infected target cells prior to introduction of the virus to lymph nodes and subsequent systemic proliferation.^{xxii}

Summary

Although the management of HIV-infected patients may seem complicated and intimidating, familiarity with the most common opportunistic infections will facilitate their care. Because many people infected with HIV are unaware of their serologic status, it is important to consider the possibility of HIV in any patient who presents with complaints suggestive of opportunistic or unusual infection. The ED clinician must assess the patient's risk for such infections and look for

Risk Management Pitfalls For Managing HIV-Infected Patients In The ED

1. **"I didn't know the patient had HIV."**

Many patients who present with AIDS-related complications have not previously been diagnosed with HIV. HIV should always be considered in patients with possible infection, especially pneumonia and CNS infections. When you see an adult with oral thrush, think HIV.

2. **"The chest x-ray was negative."**

PCP and TB can have subtle presentations, and the chest x-ray is sometimes negative early in the course of illness. Oxygen desaturation with exercise or increased A-a gradient may be clues to early PCP.

3. **"The infiltrate on the chest x-ray looked lobar, so I didn't treat for PCP."**

Chest x-ray cannot reliably determine the etiology of pneumonia. Do not exclude PCP, bacterial pneumonia, or TB based on radiographic appearance. In patients with immunosuppression due to HIV, TB usually does not have the classic appearance of apical infiltrate or cavitation. It is commonly misdiagnosed as bacterial pneumonia or PCP. Ideally, all admitted HIV patients with pneumonia should be isolated until TB is ruled out.

4. **"I sent him home because I know PCP can be treated on an outpatient basis."**

True, but this gentleman had a pulse ox of 87% and was homeless. Because patients with PCP can sometimes deteriorate despite therapy, outpatient therapy is recommended only in suitable candidates with ensured follow-up.

5. **"The patient didn't have any meningeal signs."**

Most patients with cryptococcal meningitis do not have meningeal signs. Fever and/or headache are the most common presenting symptoms.

6. **"The CSF profile was unremarkable."**

CSF glucose, protein, and cell counts are often normal with cryptococcal meningitis. An India ink stain will identify about 75% of cases. Cryptococcal antigen is the most sensitive test, but results may not be available until the next day.

7. **"The patient had no focal deficits, so I didn't do a CT scan."**

Patients with CNS lesions due to toxoplasmosis or other etiologies often do not exhibit focal findings on neurologic examination. A CT scan should be performed prior to LP in patients with immunosuppression due to HIV.

8. **"I didn't see any findings on ophthalmoscopic exam."**

CMV retinitis often involves the peripheral retina in early stages. Treatment will prevent further visual loss but is not very effective in reversing retinal damage. It is important to promptly refer HIV patients with visual complaints for full evaluation by an ophthalmologist.

9. **"I thought the fever was just due to a simple viral syndrome."**

A new fever or change in fever pattern in an AIDS patient warrants investigation. Common causes of fever without an apparent source include occult pneumonia (including PCP), CNS infection, TB, disseminated MAC, lymphoma, and drug reactions.

10. **"I didn't know what medications he was taking."**

Patients with HIV are often taking complicated drug regimens. Many of the drugs have severe toxicities that must be considered when patients present with emergent complaints. Available sources of data may include old records, a call to the patient's home to collect pill bottles, pharmacy records, and the primary care provider.

common sources of infection such as lungs and CNS. Don't hesitate to use your consultants, since management of HIV infection is a rapidly changing field.

Case Conclusion

With a sinking feeling, you realized the patient before you had the clinical hallmarks of middle to late HIV infection. You quickly attempted to remember the details of the recent Emergency Medicine Practice article on "HIV-Related Illnesses" as you discussed your concerns with the patient. You completed a thorough history and physical examination and noted that he had an accompanying headache and diplopia with his fever. He was currently not taking any medications. There was also a mild cough. His physical examination produced pertinent positives of right-sided weakness.

Thanks to the recent implementation of ED HIV testing, the patient agreed to the HIV testing and admission for the workup of his fever. You ordered chest and head radiographic imaging as you realized that the most common etiology of fever in HIV patients is pulmonary-related. However, given his neurological exam, you surmised a CNS cause - including lymphomas, toxoplasmosis, etc. At the time, your early decision to admit based on initial findings allowed the inpatient team to take over care as you ran upstairs to manage a floor-airway issue. You hoped medical intervention was in time to help him.

References

Evidence-based medicine requires a critical appraisal of the literature based on study methodology and number of participants. Not all references are

Table 5. Recommended HIV Postexposure Prophylaxis For Percutaneous Injuries

Exposure Type	Infection Status of Source				
	HIV-Positive Class 1*	HIV-Positive Class 2*	Source of Unknown HIV Status†	Unknown Source§	HIV-Negative
Less Severe¶	Recommend basic 2-drug PEP	Recommend expanded 3-drug PEP	Generally, no PEP warranted; however, consider basic 2-drug PEP** for source in settings where HIV risk factors††	Generally, no PEP warranted; however, consider basic 2-drug PEP** in settings where exposure to HIV-infected persons is likely	No PEP warranted
More Severe§§	Recommend expanded 3-drug PEP	Recommend expanded 3-drug PEP	Generally, no PEP warranted; however, consider basic 2-drug PEP** for source with HIV risk factors††	Generally, no PEP warranted; however, consider basic 2-drug PEP** in settings where exposure to HIV-infected persons is likely	No PEP warranted

* HIV-positive, class 1: asymptomatic HIV infection or known low viral load (eg, ≤ 1500 RNA copies/mL). HIV-positive; class 2: symptomatic HIV infection, AIDS, acute seroconversion, or known high viral load. If drug resistance is a concern, obtain expert consultation. Initiation of postexposure prophylaxis (PEP) should not be delayed pending expert consultation, and, because expert consultation alone cannot substitute for face-to-face counseling, resources should be available to provide immediate evaluation and follow-up care for all exposures.

† Source of unknown HIV status (eg, deceased source person with no samples available for HIV testing).

§ Unknown source (eg, a needle from a sharps disposal container).

¶ Less severe (eg, solid needle and superficial injury).

** The designation "consider PEP" indicates that PEP is optional and should be based on an individualized decision between the exposed person and the treating clinician.

†† If PEP is offered and taken and the source is later determined to be HIV-negative, PEP should be discontinued.

§§ More severe (eg, large-bore hollow needle, deep puncture, visible blood on device, or needle used in patient's artery or vein).

Source: No authors listed. Updated U.S. Public Health Service Guidelines for the Management of Occupational Exposures to HBV, HCV, and HIV and Recommendations for Postexposure Prophylaxis. *MMWR Morb Mortal Wkly Rep* 2001 Jun 29;50(RR11):1-42. Table 4. (Go to <http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5011a1.htm> for the full text recommendations.)

equally robust. The findings of a large, prospective, randomized, blinded clinical trial should carry more weight than a case report.

To help the reader judge the strength of each reference, pertinent information about the study, such as the type of study and the number of patients in the study, is included in bold type following the reference, where available. In addition, the most informative references cited in this chapter, as determined by the authors, are noted by an asterisk (*) next to the number of the reference.

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Key Points For HIV-Related Emergencies

- Assess for HIV risk factors in patients with unknown HIV status.
- Consider the possibility of occult HIV infection and possible opportunistic infection in any patient presenting to the ED with symptoms of infection.
- Assess the risk of opportunistic infection using past medical history, CD4 counts, absolute lymphocyte count, and physical signs such as thrush, Kaposi's sarcoma, and weight loss.
- Watch for subtle presentations of PCP.
- Consider TB in all HIV patients with respiratory infection, and isolate patients who are admitted for pneumonia.
- Liberally apply PPDs to those treated as outpatients.
- Treat for possible bacterial infection in patients

who appear to have PCP.

- Obtain CNS imaging prior to LP in HIV patients presenting with headache or altered mental status. Check the opening pressure when performing the LP.
- Watch for subtle presentations of cryptococcal meningitis.
- Meningeal signs are absent in most, and CSF may appear normal on routine studies.
- Refer AIDS patients with visual complaints for ophthalmology evaluation promptly, even if the retina appears normal on funduscopy.
- For AIDS patients with unexplained fever, consider the most likely sources first—lungs and CNS.
- Watch for drug toxicities.

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CME Questions

- 33. A total lymphocyte count of less than 1000/mm³ is:**
- Unlikely to be associated with a CD4 count of less than 200/mm³
 - Likely to be associated with a CD4 count of less than 200/mm³
 - Diagnostic of AIDS
 - Not at all predictive of CD4
- 34. PCP prophylaxis with TMP-SMX is now standard for:**
- Any patient with HIV infection
 - A patient with HIV and a history of tuberculosis
 - A patient with HIV and a CD4 count below 500/mm³
 - A patient with HIV and a CD4 count below 200/mm³
- 35. The diagnosis of PCP may be aided by:**
- An exercise-induced decrease in oxygen saturation
 - A Gram stain of an expectorated sputum sample
 - Finding an LDH level in the normal range
 - A routine blood culture
- 36. All of the following are common etiologies of fever in AIDS patients EXCEPT:**
- Herpes simplex
 - P jiroveci* and other pneumonias
 - Sinusitis
 - Cryptococcal meningitis
 - Bacteremia/sepsis
- 37. Which of the following factors is associated with an increased risk of HIV infection?**
- Injection drug use
 - Prostitution
 - Heterosexual exposure to a partner at risk
 - Children born of mothers in a risk group
 - All of the above
- 38. A 30-year-old white male with a history of HIV infection for 5 years and a recent CD4 count of 78/mm³ presents to your ED complaining of a mild-to-moderate headache, nausea, and fever. He has a previous history of cryptococcal meningitis 2 years ago but is not taking any medications now. His neurological examination is normal; he has no meningismus, but he does have a temperature of 39°C (102.2°F).**
- Cryptococcal meningitis is very unlikely if the patient has completed a 6-month course of fluconazole after the previous infection.
 - A lumbar puncture is indicated, but it can wait until after a CT scan rules out mass lesions (such as caused by toxoplasmosis and lymphoma).
 - Cryptococcal meningitis is unlikely because he has no meningismus or neurological examination abnormalities.
 - CSF analysis will usually reveal greater than 20 white blood cells/mm³ if the patient has cryptococcal meningitis.
 - It is not useful to send the CSF for India ink stain or cryptococcal antigen test, as these tests take too long for an ED diagnosis.

39. All of the following are true EXCEPT:
- The finding of oral candidiasis or hairy leukoplakia in a patient with a fever suggests an HIV-related illness
 - Thrush is a sure sign of HIV infection
 - Patients with oral lesions tend to have low CD4 counts and fast disease progression
 - Other causes for oral candidiasis include out-of-control diabetes, recent antibiotic or inhaled steroid use, or chemotherapy
40. Patients with AIDS and presumed toxoplasmosis:
- Rarely receive an immediate diagnosis, because the disease progresses very quickly
 - Should be admitted and treated with pyrimethamine and sulfadiazine, or pyrimethamine and clindamycin for those with sulfa allergies
 - Should not receive steroids if significant surrounding edema is found
 - Are easily curable with appropriate therapy
41. Patients with AIDS and chronic diarrhea:
- Rarely develop debilitating illness, as the diarrhea is usually mild
 - Should never be treated with diphenoxylate or loperamide, because decreasing gut motility in intestinal infections is life-threatening
 - Due to *Cryptosporidium* can often be cured with a prolonged course of TMP-SMX
 - Should have stool studies performed if they develop a significant change in the pattern of their diarrhea
42. A patient with AIDS presents with complaints consistent with esophagitis and dysphagia. Which of the following statements is true?
- The most common organism causing this condition is the herpes simplex virus.
 - Any antimicrobial therapy, such as oral fluconazole, should be preceded by esophagoscopy and biopsy.
 - Oral topical solutions for thrush, such as nystatin or clotrimazole troches, will reliably treat esophageal candidiasis.
 - Particularly resistant or severe esophageal candidiasis may require inpatient treatment with amphotericin B.
43. All of the following statements regarding drugs for HIV therapy are true EXCEPT:
- A patient experiencing a rash with abacavir may be safely continued on his or her medication but may require antihistamine therapy for comfort
 - Efavirenz is associated with a variety of CNS symptoms, including abnormal dreams and altered mental status
 - Zidovudine (AZT) is associated with anemia and agranulocytopenia
 - Patients taking indinavir who develop sudden-onset flank pain and fever need a CT scan of their urinary tract
44. Tuberculosis in AIDS patients:
- Often presents atypically
 - Is very rare
 - Doesn't require isolation
 - Generally produces the same chest x-ray findings as it does in the general population
45. Which of the following can cause diarrhea in AIDS patients?
- Bacterial pathogens such as *Salmonella*, *Shigella*, and *Campylobacter*
 - Parasitic, mycobacterial, or viral infection, including *Giardia lamblia*, *Cryptosporidium parvum*, and *Isospora belli*
 - Cytomegalovirus
 - Antimicrobials the patient is taking
 - All of the above
46. When treating PCP:
- Steroids are not useful as adjunctive therapy for severe PCP.
 - Although dapsone can cause hemolytic anemia in patients who are G6PD-deficient, it is the drug of choice for treating inpatient PCP.
 - Patients with a mild rash while on TMP-SMX for severe PCP may often be safely treated through the rash, although they may require antihistamines for comfort.
 - TMP-SMX causes a rash in up to 50% of patients, but hematological abnormalities are very rare.

Antibiotics In The ED: How To Avoid The Common Mistake Of Treating Not Wisely, But Too Well

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CME Objectives

Upon completing this article, you should be able to:

1. Discuss important factors in choosing antibiotics for ED use.
2. Describe the important characteristics of the classes of antibiotics most commonly used in the ED.
3. Identify and discuss common clinical and medicolegal problems and pitfalls that occur when treating infections in the ED.
4. Choose appropriate antibiotics for the infections most commonly encountered in the ED.

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*"In mortal combat you must choose the right weapon and wield it well."
—Chinese proverb*

Diary From The ED

10/05 — I saw a 75-year-old woman today; she came in for fever, cough, lower back pain, and "not feeling well." She said she had been ill for several days. In triage, she had a temperature of 38°C (101°F) respirations 18, blood pressure 140/80, pulse 108, and oxygen saturation 98%. Her physical exam was completely normal. I thought she probably had bronchitis, and discharged her home on azithromycin (Z-pack)...

10/07 — What an awful day! This 75-year-old woman from a couple of days ago was brought in by EMS complaining of fever, back and abdominal pain, and generalized weakness. She said that she had been feeling worse and worse, despite taking the antibiotic I gave her. She was febrile (39°C [102.8°F]) hypotensive (80/60), tachycardic (140), and she had lower abdominal tenderness. I ordered all the tests and cultured her. She turned out to have urosepsis. Her pressure was dropping and we had to intubate her. I have to check on her in the unit tomorrow ... Reminder: also check on liability coverage.

Clinicians working in the ED are on the frontlines in the war against infections. A decisive and focused early assault here can prevent future losses. ED clinicians face the dilemma of choosing the right antibiotic for treatment of infections many times during any single shift. This choice is often influenced by tradition, personal preferences, advertising by pharmaceutical companies, commonly used

references, such as *The Sanford Guide to Antimicrobial Therapy*¹, pharmaceutical company advertising, and occasionally — but perhaps not often enough — scientific evidence. We may tend to choose antibiotics that are broad-spectrum, high-profile, and more expensive, but these are not always in the best interest of a given patient.

Clinicians who treat infectious diseases in the ED need to apply a vast amount of knowledge regarding not only which antibiotics are appropriate in a particular situation, but also the relevant microbiology, diagnostic testing, and pathophysiology of the underlying disease. In everyday practice, it is not feasible to do a "bedside" literature search that would take all these factors into account. Most of us rely on memory or a guidebook, or both, but we cannot always be certain about the validity of the scientific studies on which we base our decisions. In this article we will move onto firmer ground by distilling some of the existing evidence into concise practical guidelines.

Critical Appraisal Of The Literature

Although the body of literature on antibiotics is vast, the quality of the information reported varies widely. The best evidence we found came from the Cochrane Database of Systematic Reviews,² which offers information about the strength of the evidence supporting each conclusion and allows users to assess the validity of the meta-analyses. Another important source of information proved to be the practice guidelines developed by specialty societies and expert panels, such as the guidelines for treating community-acquired

pneumonia, published by the American College of Emergency Physicians.³ A third resource was the National Guideline Clearinghouse™ (<http://www.guidelines.gov>), which was created by the Agency for Healthcare Research and Quality (AHRQ), US Department of Health & Human Services, in partnership with the American Medical Association and America's Health Insurance Plans (AHIP) (formerly the American Association of Health Plans).⁴

Finally, an enormous amount of information can be obtained from other sources, ranging from case reports to well-designed randomized, double-blind studies. Many of the studies cited in this chapter came from a search of the literature using www.pubmed.gov.¹ In preparing this chapter, we have taken great care in interpreting the strength of the evidence provided by these sources and in formulating recommendations based on the best available information. **Table 1** provides a list of recommendations for treating some of the more common infections that confront practicing ED clinicians.

Epidemiologic Considerations

Antibiotics are among the most frequently prescribed and administered drugs in the ED. According to data collected from the 2000 National Hospital Ambulatory Medical Care Survey (NHAMCS), antibiotics were the second most frequently administered drugs in the ED (14.6%), exceeded by medications for pain relief (32%).⁵ For comparison, in the 2008 NHAMCS survey, antibiotic usage remained unchanged at 14.6%, whereas the use of analgesics had risen to 36.8%. Infections were among the most common primary admitting diagnoses: pneumonia (4.3%), cellulitis/abscesses (1.8%), and urinary tract infections (1.8%). Among all diagnoses in children

under 15 years of age, the most common final diagnoses, in decreasing frequency, were acute upper respiratory infections (URIs) (excluding pharyngitis), otitis media, and fever of unknown origin.ⁱⁱ

Etiology And Differential Diagnosis Of Infection

Although a vast array of organisms can lead to an ED visit, including viruses, bacteria, atypical organisms (eg, rickettsia, chlamydia, and mycoplasma), protozoa, fungi, and helminths, the leading offenders are the viruses. Most URIs and diarrheal syndromes are caused by viruses and usually constitute benign, self-limited infections that require only symptomatic treatment; however, one cannot discount the more serious viral infections such as encephalitis, hepatitis, and AIDS.

Treatment Of Infections Other Than Bacterial

The current therapeutic armamentarium against viruses is not as extensive as that against bacteria, but it is growing. Although not commonly administered in the ED, intravenous (IV) antiviral therapy may be lifesaving, as in the treatment of herpes encephalitis or varicella pneumonia. (See **Table 2**.)⁶ Several antiviral agents are currently under investigation for the treatment of coronavirus and rhinovirus infections, the most frequent causes of the “common cold.” One such drug is pleconaril, which had been rejected by the Food and Drug Administration (FDA) in 2001 because of safety concerns but has now been re-licensed and is being studied in a Phase II trial. This novel antiviral agent prevents replication of the virus by binding to a hydrophobic pocket within the

Table 1. Infectious Disease Treatment Recommendations Relevant To Emergency Medicine

Disease	Treatment
Acute Otitis Media	Amoxicillin should be the first-line antibiotic for acute otitis media. If this fails, next treat with amoxicillin-clavulanate, oral cefuroxime acetil, and intramuscular ceftriaxone. ¹¹⁸
Sinusitis	Mild to moderate cases of bacterial sinusitis do not require antibiotics. ¹¹⁹
Pharyngitis	1. Sore throat associated with stridor or respiratory difficulty is an absolute indication for admission to the hospital. ¹²⁰ 2. Physical examination findings, such as fever, exudate, cervical adenopathy, and palatal petechiae, increase the likelihood of having culture-confirmed strep throat. ¹²¹ The suggestion is that these findings be used along with the results of RADT or throat culture and the clinician's own judgment in deciding whether to treat with antibiotics.
Community-acquired Pneumonia	Patients with community-acquired pneumonia should be stratified according to risk. ¹²² Outpatient treatment includes a macrolide, doxycycline, or a fluoroquinolone with enhanced susceptibility for <i>S pneumoniae</i> . Hospitalized patients on the wards should receive either a fluoroquinolone alone, or a third-generation cephalosporin (ceftriaxone, cefotaxime) plus a macrolide.
Urinary Tract Infection	Urine cultures are not recommended in most cases of uncomplicated UTIs in adults. However, children diagnosed with UTI may initially have a negative urinalysis, but positive urine cultures. Therefore, a urine culture should always be obtained in children and followed up, even if treated empirically. ¹²³

Abbreviations: RADT, rapid antigen detection testing; UTI, urinary tract infection.

capsid, thus blocking its uncoding and attachment.⁷ In 1 randomized, double-blind, placebo-controlled study involving 1363 patients with the “common cold,” pleconaril led to a decrease in the intensity as well as the duration of symptoms by an average of 1 day. However, the patients whose condition improved with pleconaril were found to have picornavirus infection on culture. When cultures did not indicate picornavirus, there was no difference in efficacy between pleconaril and placebo.⁸ Only about 65% of colds are caused by picornaviruses, so if and when this medication is approved, the ED clinician must determine whether reducing symptoms for a single day would justify the cost of a medication that may be ineffective 35% of the time.

Table 2. Drugs For Treatment Of Viral Infections

Viral Infection	Drug of Choice*
Cytomegalovirus (CMV)	Ganciclovir Foscarnet Cidofovir Fomivirsen†
Hepatitis B and C (chronic hepatitis)	Interferon alfa-2b Interferon alfa-2a‡ Interferon alfacon-1‡ Ribavirin§ Lamivudinell
Herpes Simplex Virus (HSV)	Acyclovir Penciclovir¶ Famciclovir Valacyclovir Foscarnet# Trifluridine**
Human Immunodeficiency Virus (HIV)	Reverse transcriptase inhibitors (nucleoside analogs and nonnucleoside agents)†† Protease inhibitors††
Influenza A and B Viruses	Zanamivir Oseltamivir
Influenza A Virus	Rimantadine Amantadine
Respiratory Syncytial Virus (RSV)	Ribavirin
Varicella Zoster Virus (VZV)	Acyclovir Valacyclovir Famciclovir Foscarnet#

*First choice appears in bold.

†Intravitreal therapy

‡Hepatitis C only

§In combination with interferon alfa-2b for hepatitis C

*Hepatitis B only

¶Cream for orolabial lesions

#For acyclovir-resistant strains

**Ophthalmic drops

††Multiple agents available

During the 2009-2010 swine flu pandemic, oseltamivir was used to treat many persons with flulike illnesses and as chemoprophylaxis for those at higher risk (eg, the very young, those with poorly controlled asthma). Since no prospective study has been carried out during a pandemic, and the efficacy of oseltamivir is still a matter of debate, many healthcare professionals have proposed stockpiling this drug in the event of a more widespread outbreak of influenza.ⁱⁱⁱ

Infections with protozoa and fungi such as pneumocystis, cryptosporidium, and cryptococcus are commonly encountered in immunocompromised hosts, whereas in normal hosts the more common protozoan infections include malaria, amebiasis, trichomoniasis, and giardiasis. Malaria should always be considered when a recent traveler or immigrant from a developing country presents to the ED with unexplained fever. The most commonly encountered fungal infections are those due to *Candida* species and dermatophytes. Table 3 lists the more common fungal and protozoal infections, along with available treatments.^{9,10}

Since the most common antimicrobial agents used in the ED are antibacterials, these will be the focus of this chapter. For purposes of this discussion, it

Table 3. Most Commonly Encountered Protozoal And Fungal Infections

Organism	Treatment*
Protozoa	
Entamoeba	Metronidazole , tinidazole, paromomycin
Giardia	Metronidazole , albendazole, tinidazole
Plasmodia species (malarial)	Chloroquine, primaquine, quinine, doxycycline, mefloquine, pyrimethamine/sulfadoxine
Pneumocystis	Trimethoprim-sulfamethoxazole , pentamidine, primaquine, clindamycin, dapsone†
Toxoplasma	Pyrimethamine/sulfadiazine , trimethoprim-sulfamethoxazole, clindamycin
Trichomonas	Metronidazole
Fungi‡	
Candida	Clotrimazole§, miconazole§, fluconazole*¶, amphotericin*†
Cryptococcus	Amphotericin B , fluconazole#, flucytosine**
Dermatophyton	Clotrimazole§, ketoconazole§, miconazole§††

*First choice appears in bold.

†Only some of the available treatments listed

‡The most common in the ED

§Topical

*IV treatment for bloodstream and other serious infections

¶Oral formulations available

#Oral or IV

**Adjunct to amphotericin

††Alternative and oral treatments available

is useful to categorize bacteria into 4 types of organisms: gram-positive, gram-negative, anaerobic, and atypical (chlamydia, mycoplasma, and rickettsia). This categorization will help the ED clinician choose the right class of antibiotics for the best coverage. A summary of the most commonly used classes of antibiotics and the categories of bacteria they cover is presented in **Table 4**.

Pharmacology Of Antibiotics

Antibiotics can kill bacteria or inhibit their growth through various mechanisms of action. These include inhibiting synthesis of the cell wall, proteins, DNA, and/or RNA; interfering with folate metabolism; and producing free radicals. The mechanisms of action for the most important classes of antibiotics are outlined in **Table 4, pages 91-92**.^{9,10}

An important property of any antibiotic is whether it is bactericidal or bacteriostatic — that is, whether it kills the enemy or merely takes it prisoner and prevents it from multiplying. This property is of particular importance in serious infections such as endocarditis, meningitis, or neutropenia. Clindamycin, which covers *Streptococcus viridans* and *Staphylococcus aureus*, does not adequately treat endocarditis caused by these organisms because it is a bacteriostatic agent. It is believed that the reason for its failure is the inability of macrophages to penetrate the vegetations and kill the organisms, which replicate more slowly because of the action of clindamycin.

Also important is the ability of an antibiotic to reach the site of infection in concentrations high enough to kill the invader. For example, although *Klebsiella pneumoniae* is usually very sensitive to gentamicin, this drug is actually a poor choice for treating *K pneumoniae* infection because it does not reach sufficient levels in the lung parenchyma to destroy the organism. Likewise, many antibiotics, such as first-generation cephalosporins, may adequately kill a pneumococcus such as *Streptococcus pneumoniae* in vitro, but they cannot be used to treat pneumococcal meningitis because they do not penetrate the blood-brain barrier.

The absorption of a drug determines the best route of its administration. A striking example of this is oral vancomycin, which cannot be used to treat most infections (eg, cellulitis or endocarditis) because it is not absorbed via the gastrointestinal tract. However, the oral preparation can be used to treat pseudomembranous colitis caused by *Clostridium difficile*.

Remaining factors that require consideration are the metabolism and excretion of antibiotics. In patients with renal disease, dose adjustments will be required for those antibiotics with active or toxic metabolites that are excreted by the kidneys. Likewise,

when treating patients with liver disease, certain hepatically metabolized antibiotics should be avoided so that drug levels do not rise to the toxic range. A classic example of this is the use of chloramphenicol in newborns, which results in the “gray baby” syndrome. Because the neonate’s liver is immature, it does not yet produce the enzymes necessary to metabolize this drug. **Table 5 (see page 93)** lists a number of antibiotics that require dose adjustments in patients with renal or liver disease.^{1,9}

In this age of globalization and travel, clinicians should also be aware of the indications for and safety profiles of antibiotics that are used less frequently in the US (for a variety of reasons) but are more commonly prescribed in less affluent countries. Clinicians who practice in or near areas with a high immigrant population should recognize signs of toxicity resulting from the use of a less-familiar or rarer antibiotic. Returning to the previous example of chloramphenicol and its side effects (which also include aplastic anemia and bone marrow suppression), the World Health Organization (WHO) recommends chloramphenicol as the first-line agent against meningitis because of its relatively low cost (\$5 [US] per course of treatment).^{iv,v}

Preventive Measures For Healthcare Providers

The most important aspect of managing patients suspected of having a severe infection is proper attention to the airway, breathing, and circulation — the ABCs of emergency care. In addition, given the nature of infections, special precautions need to be taken by hospital personnel. When Hippocrates said, “Primum non nocere” (first, do no harm), it was certainly intended to remind us to avoid harming ourselves as well as others.

Prehospital care providers, EMS personnel, and ED staff are exposed to infectious diseases on a daily basis. Certain preventive measures should be followed to minimize the risk of contracting or transmitting a serious infection. Since most prehospital and hospital personnel do not initially know a patient’s infectious status, certain universal precautions should always be followed as a matter of routine. These include taking steps to avoid contamination with blood, respiratory secretions, vomitus, urine, and feces.

All EMS providers and healthcare professionals must wear disposable gloves when exposure to contaminated body fluids is anticipated. Gloves, gowns, and masks should be worn when respiratory infections are suspected. Also, any refuse contaminated with blood or other body fluids such as feces, saliva, sputum, or vomitus should be disposed of in properly labeled biohazard bags.¹¹ Frequent hand-washing is the single best method for preventing the spread of infection. As a general rule, healthcare

Table 4. Brief Characteristics Of The Most Commonly Used Antibiotics

Class	Mechanism of Action	Metabolism and Excretion	Bacteria Covered
Penicillins (natural) (penicillin G, pen VK)	Bactericidal Inhibit cell wall synthesis	Excreted in urine mostly in intact form	Gram (+) , except staph Some anaerobes <i>N meningitides</i>
Penicillinase-resistant penicillins (methicillin, nafcillin, dicloxacillin)	Bactericidal Inhibit cell wall synthesis	Excreted in bile and urine	Gram (+), used mostly for staph, but not MRSA
Aminopenicillins (ampicillin, amoxicillin)	Bactericidal Inhibit cell wall synthesis	Some bile excretion, but mostly kidney	Gram (+) , but not MRSA Some gram (-) , not <i>Pseudomonas</i> Some anaerobes
Aminopenicillins with betalactamase inhibitor (ampi/subactam, amoxi/clavulanate)			Better staph coverage Better gram (-) and anaerobic coverage
Antipseudomonal penicillins (ticarcillin, azlocillin, mezlocillin, piperacillin)	Bactericidal Inhibit cell wall synthesis	Excreted in bile and urine	Gram (+) , but not staph Some gram (-) Some anaerobes
Anti-pseudomonal penicillins with beta-lactamase inhibitor (ticarcillin/clavulanate, piperacillin/tazobactam)			Better staph coverage Better gram (-) and anaerobic coverage
Monobactams (aztreonam)	Bactericidal Inhibit cell wall synthesis	Excreted mostly in urine	Gram (-) , including <i>Pseudomonas</i> No Gram (+) or anaerobes
Cephalosporins first-generation (cephalexin, cefazolin, cephadrine)	Bactericidal Interfere with cell wall synthesis	Excreted mostly intact in urine	Gram (+) , not MRSA Some gram (-) Some anaerobes
Cephalosporins second-generation (cefuroxime, cefoxitin, cefotetan, cefaclor, cefprozil)			Gram (+) , not MRSA Gram (-) , not <i>Pseudomonas</i> Anaerobes
Cephalosporins third-generation (ceftriaxone, cefotaxime, ceftazidime, cefixime)			Gram (+) , not MRSA Gram (-) , most are weak against <i>Pseudomonas</i> Some anaerobes
Cephalosporins fourth-generation (cefepime)			Gram (+) , not MRSA or enterococcus Gram (-)
Carbapenems (imipenem, meropenem)	Bactericidal Inhibit cell wall synthesis	Excreted mostly in urine	Gram (+) , not MRSA Gram (-) Anaerobes
Fluoroquinolones (ciprofloxacin, ofloxacin, norfloxacin)	Bactericidal Inhibit DNA gyrase	Some excreted by kidney, often metabolized in liver	Some gram (+) , staph but not MRSA Gram (-) Some atypicals
Extended-spectrum fluoroquinolones (levofloxacin, gatifloxacin, moxifloxacin)			Gram (+) Gram (-) Atypicals Some anaerobic coverage

Table 4. Brief Characteristics Of The Most Commonly Used Antibiotics (Continued)

Class	Mechanism of Action	Metabolism and Excretion	Bacteria Covered
Macrolides (erythromycin, azithromycin, clarithromycin)	Bacteriostatic Inhibit protein synthesis	Metabolized in liver, excreted in bile and minimally in urine	Gram (+) , but not MRSA Some gram (-) Atypicals Some anaerobes
Aminoglycosides (gentamicin, tobramycin, amikacin)	Bactericidal Inhibit protein synthesis	Excreted unchanged in urine	Staph (combine with beta-lactams) Gram (-)
Tetracyclines (tetracycline, doxycycline)	Bacteriostatic Inhibit protein synthesis	Excreted mostly in urine	Some gram (+) Some gram (-) Atypicals Some anaerobes
Clindamycin	Bacteriostatic Inhibits protein synthesis	Metabolized mostly in liver and excreted in bile	Gram (+) , not MRSA Anaerobes
Vancomycin	Bactericidal Inhibits cell wall synthesis and inhibits RNA synthesis	Excreted in urine	Gram (+) Some anaerobes
Trimethoprim/ sulfamethoxazole	Bacteriostatic Folate antagonist/inhibits folate synthesis	Metabolized in liver, excreted in urine	Some gram (+) Some gram (-) Some protozoans
Metronidazole	Bactericidal Toxic to cells by interfering with electron transport/producing free radicals	Metabolized in liver	Anaerobes Some protozoans and parasites
Chloramphenicol	Bacteriostatic Inhibits protein synthesis	Metabolized in liver, excreted by kidney	Gram (+) Gram (-) Anaerobes Rickettsia
Nitrofurantoin	Bacteriostatic or bacteriocidal depending on concentration	Metabolized in liver, excreted by kidney	Gram (+) Gram (-) Only in the lower urinary tract

providers should wash their hands with soap for at least 10 seconds after any patient contact. Finally, to prevent transmission of blood-borne infections — specifically AIDS and hepatitis B — used needles should never be recapped; they must be disposed of immediately in a clearly marked “sharps” container.

As for equipment exposed to infectious organisms, ambulances must be cleaned daily using any basic household disinfectant, in addition to a 0.5% bleach solution to wash down any blood-contaminated areas. Gloves should be worn while cleaning the rig, and a log should be maintained to document each time the ambulance is cleaned.

Evaluation In The ED

The initial steps in the evaluation and management of a patient with infection are similar to those taken for treating all emergencies. First, attend to the basics: provide airway support, if needed, for patients with hypoxemia or sepsis and deliver oxygen and circulatory support when indicated. Next, perform a complete history and physical examination, followed by the appropriate laboratory studies and cultures. Most importantly, start antibiotic therapy as soon as possible, since this step may be lifesaving.

History

To determine the etiology of a patient’s infection, the ED clinician must take a careful history and carry out a thorough physical examination. The approach should be systematic so that nothing of relevance is overlooked. **Table 6 (see page 94)** provides a summary of history and physical findings according to system. Even though a thorough history will usually lead to a correct diagnosis, it can at times be misleading. For example, sinusitis has often been associated with facial pain, pressure, and headache. However, a recent study showed that sinusitis corroborated by CT is most often associated with nasal congestion,

Table 5. Some Antibiotics That Require Dosage Adjustment In Liver Or Kidney Disease

In Renal Disease	In Liver Disease
Some cephalosporins (mostly third-generation cephalosporins)	Most cephalosporins
Clindamycin	Aminoglycosides
Chloramphenicol	Macrolides
Metronidazole	Fluoroquinolones
Nafcillin	Penicillins

fatigue, sleep disturbance, and decreased sense of smell; facial pain was the least common symptom associated with CT-confirmed sinusitis.¹²

In general, the patient’s symptoms will direct the ED clinician to the possible site of infection. Bacteriologic statistics are useful for identifying the organism most likely to cause infection in a given patient at a given site (“specific organisms like specific sites”). Microbes follow the mantra of the real estate agent: location, location, location! While the symptoms will alert you to the most likely site, the physical examination along with appropriate ancillary tests will usually help to confirm it. **Table 7 (see page 95)** presents the most common agents responsible for infections at various body sites.^{1,9}

Further clues, including time of onset, progression of symptoms, and associated events, may help differentiate among potential etiologic agents. For example, a patient with pneumonia who recently had a seizure disorder may have aspirated, thus elevating anaerobes on the list of suspects. The contaminants in a bite wound will differ from those harbored on a dirty nail. Though the clinical presentation can be useful, it might sometimes be atypical or even misleading, especially in the very young, the elderly, and the immunosuppressed. As a remarkable example, a retrospective study on the presentation of urinary tract infections (UTIs) in the elderly found that one of the most common presenting symptoms was cough!¹³

The patient’s past medical history can be critical in defining which organisms are more likely to be causing the infection. Patients without a spleen, and “functionally asplenic” patients such as those with sickle cell disease, would be prone to infection with encapsulated organisms. In such a host, *Haemophilus influenzae* and pneumococcus can cause overwhelming sepsis in a very short time. An immunosuppressed host may also harbor uncommon organisms such as *Pneumocystis jiroveci* or *Cryptococcus neoformans*.^{14,15} (Refer to Chapter 3 in this book, “HIV-Related Illnesses: The Challenge Of ED Management” for an in-depth, updated look at diseases associated with HIV-generated immunosuppression.)

Another factor to consider is where the infection was acquired. Hospital-acquired organisms tend to be more resistant to antibiotics than those coming from the community, and it is important to know the local patterns of resistance for both hospital- and community-acquired organisms. Be sure to ask if the patient has been hospitalized in the past 2 months and to inquire about communal living conditions (eg, nursing home, military barracks, dormitory). Hospital laboratories will often have information about the sensitivities of the most common organisms, and such information is crucial because of the increasing emergence of multidrug-resistant bacteria.¹⁶⁻²¹ Take, for example, resistant strains of

pneumococcus: knowing the degree to which these are present in the community and local hospitals is the key to deciding whether to prescribe penicillin, ceftriaxone, or vancomycin. Many hospitals have published antibiograms that can assist the ED clinician in choosing the most effective course of treatment for specific infectious entities.

Finally, obtaining a social history from the patient may further pinpoint the offending organism by revealing a lifestyle factor such as intravenous drug use (suggesting staphylococcal endocarditis) or alcoholism (suggesting *Klebsiella pneumoniae*).

Physical Examination

The physical examination may provide valuable diagnostic information, especially regarding the site of infection — one of the most important clues to a possible etiologic agent. For example, a child with a bullous skin lesion probably has *S aureus* infection, whereas a young, healthy woman with costovertebral angle tenderness probably has pyelonephritis due to *Escherichia coli* infection. Occasionally, highly specific physical findings will point to the etiology, such as the pathognomonic circular rash seen in Lyme disease (erythema migrans).

The physical examination begins with the vital signs. The standard first goal of emergency medicine is an aggressive approach to correct abnormal vitals. Blood pressure measurement gives an assessment of illness severity. Together with central venous pressure, it should be one of the most closely monitored parameters in patients presenting to the ED in early sepsis. In septic patients, an aggressive correction of hypotension with fluids

and pressors was shown to positively affect the outcome.²² A landmark study published in the *New England Journal of Medicine* in 2001 has streamlined early sepsis management (as Early Goal Directed Therapy) and has become standard of care in emergency medicine. While the full scope of the study is beyond this article, its importance in sepsis management cannot be understated.

Heart rate assessment is a rapid and very inexpensive test. It can point the ED clinician towards a diagnosis of infection or even sepsis. Unexplained tachycardia should prompt a temperature and blood pressure check. On the other hand, relative bradycardia in a hypotensive or febrile patient can sometimes give a clue to the specific etiology of an infection (eg, salmonella sepsis). Temperature can be measured in various ways: oral, tympanic, or rectal. The tympanic thermometer has been shown to be poorly sensitive for fever compared to the rectal. In a study of 332 patients presenting to the ED, the correlation of rectal and oral temperature measurements was 0.94, while the tympanic thermometer failed to detect 9 out of 28 febrile patients.²³

However, a more recent study looking at 400 neutropenic adults suggests that a single tympanic membrane reading was more sensitive than oral or axillary readings in detecting rectal fever.^{vi}

A rectal temperature is therefore indicated in patients who are uncooperative or dehydrated, or those who are mouth breathing.^{24,25} It should also be utilized in the elderly or the very young and in cases when clinicians have a high suspicion of hypothermia/fever that was not elicited on axillary or oral temperature.

Table 6. Systematic Approach To History And Physical Examination

System	History	Physical Findings
General	Fatigue, weight loss, fever (how high, duration, method of measurement), anorexia, chills, rigors	Cachexia, nutritional status, dry mucous membranes
HEENT	Headache, earache, ear discharge, nasal congestion, rhinorrhea (color), facial pain, sore throat, dysphagia	Fluid behind ear drum, decreased mobility on insufflation, facial tenderness, pharyngeal erythema, tonsillar exudates, sinus transillumination
Neck	Tenderness, rigidity	Supple, adenopathy
Heart	Chest pain	Tachycardia, murmur, rub
Lungs	Shortness of breath, cough, sputum (color), pleuritic chest pain	Rales, rhonchi, bronchial breath sounds
Abdomen	Abdominal pain (location), nausea, vomiting, diarrhea, blood in stool	Tenderness, rebound, blood on fecal occult blood examination
Genitourinary	Dysuria, frequency, urgency, hematuria	Tender prostate, urethral discharge, penile lesions, inguinal adenopathy, Fournier's gangrene
Skin	Rash, pruritus	Rashes, petechiae, signs of cellulitis, ulcers
Musculoskeletal	Joint pain, swelling, erythema	Joint edema, erythema, effusion
Neurologic	Headache, photophobia, altered behavior, weakness, nerve palsies	Altered mental status, ataxia, motor/sensory abnormalities, meningismus, seizures, papilledema

Pulse oximetry, long regarded as the “fifth vital sign,” has the appeal of an objective and inexpensive way to assess breathing and oxygenation. As long as its limitations are kept in mind (ie, its dependence on tissue perfusion, ambient temperature, skin color, presence of nail polish), it is an excellent tool that gives more information than respiratory rate alone.

When evaluating a patient, the physician must pay close attention to the patient’s mental status. Both systemic and central nervous system infections cause delirium. One study followed 171 elderly patients admitted to a hospital with a presenting diagnosis of delirium and found that the most common cause of delirium was infection (34%), particularly pneumonia and urinary tract infections.²⁶ For more details pertaining to the physical examination, see Table 6.

A neurological examination is extremely important in HIV-seropositive patients. Altered mental status may be the only presenting symptom in a patient who has a new-onset CNS pathology, such as toxoplasmosis encephalitis.^{vii} Clinicians should also attempt to obtain a thorough history from family members, friends, etc regarding the time course of the mental status change. Neurological changes (along with age) is a poor prognostic factor in these patients.

Diagnostic Testing

Chemistry Panel

The chemistry panel can occasionally offer clues to the etiology of an infection, as in the case of an elderly patient with cough, fever, hyponatremia, and elevated liver function tests (LFTs), possibly indicating *Legionella* pneumonia. Additionally, the chemistry panel may show the hydration status, renal function, and acid-base status of the patient.

Complete Blood Count

Although an elevated white blood cell count (WBC) is associated with infection, its predictive value for bacterial disease has proven to be low.^{27,28} Serious bacterial illnesses may present with a normal WBC count, and elevated counts are often due to causes other than bacteria, such as viral infections. This test may be helpful when following a known abnormality or looking for an expected effect, such as drug-induced leukopenia. A decrease in leukocytes may be seen in certain bacterial infections, such as typhoid fever.²⁹

There are conflicting data as to whether a high neutrophil count on the differential correlates with bacterial infection.^{30,31} However, it has been shown

Table 7. Etiology Of The Most Common Bacterial Infections Encountered In The ED

Site of Infection	Pathogen
Dental/odontogenic infections	Streptococcus, anaerobes, staphylococcus
Pharyngitis	Group A streptococcus, group C streptococcus, group G streptococcus
Otitis media	<i>S pneumoniae</i> , <i>H influenzae</i> , <i>M catarrhalis</i>
Sinusitis	<i>S pneumoniae</i> , <i>H influenzae</i> , <i>M catarrhalis</i> , group A streptococcus, anaerobes
Bronchitis (acute exacerbation of chronic bronchitis)	<i>S pneumoniae</i> , <i>H influenzae</i> , <i>M catarrhalis</i>
Pneumonia	Newborns: Group B streptococcus, enterobacteriaceae, <i>Listeria</i> , <i>Chlamydia</i> Age less than 5: <i>S pneumoniae</i> , <i>H influenzae</i> , <i>S aureus</i> , <i>M pneumoniae</i> Age 5-18: <i>S pneumoniae</i> , <i>M pneumoniae</i> , <i>Chlamydia</i> Adults: <i>S pneumoniae</i> , <i>M pneumoniae</i> , <i>Chlamydia</i> , <i>M catarrhalis</i> , <i>H influenzae</i>
Urinary Tract Infection	Enterobacteriaceae (<i>E coli</i>), <i>S saprophyticus</i> , <i>Proteus</i> sp, <i>Klebsiella</i> , enterococci
Pelvic inflammatory disease	<i>N gonorrhoeae</i> , <i>C trachomatis</i> , anaerobes, enterobacteriaceae
Intra-abdominal infections	Enterobacteriaceae, enterococci, <i>Bacteroides fragilis</i> , clostridia
Gastrointestinal (bacterial diarrhea)	<i>Shigella</i> , <i>Salmonella</i> , <i>E coli</i> , <i>Campylobacter jejuni</i> , <i>Yersinia enterocolitica</i>
Skin	Cellulitis: <i>S aureus</i> , <i>Streptococcus pyogenes</i> , group A streptococcus Bite wounds: <i>S viridans</i> , <i>Pasteurella multocida</i> , <i>S aureus</i> , <i>Eikenella corrodens</i> Diabetic foot: Aerobic cocci and bacilli, anaerobes
Meningitis	Neonates: Group B streptococcus, <i>E coli</i> , <i>Listeria</i> Age 1-50: <i>S pneumoniae</i> , <i>N meningitidis</i> , <i>H influenzae</i> Older than 50: <i>S pneumoniae</i> , <i>Listeria</i> , enterobacteriaceae
Endocarditis	Native valves not IVDU: <i>S viridans</i> , staphylococci, enterococci IVDU: <i>S aureus</i> Artificial valves: <i>Staphylococcus epidermidis</i> , <i>S aureus</i> , <i>S viridans</i>

Abbreviation: IVDU, intravenous drug user.

that the differential can reliably discriminate between viral and bacterial infections in very young children (under 3 months of age).³² The WBC count will determine whether antibiotics should be prescribed for previously healthy, well-appearing children 3 to 36 months of age who present with a rectal temperature of $\geq 39.0^{\circ}\text{C}$ (102.2°F) without a known source. The current recommendation³³ is to consider antibiotic therapy in these children when the WBC count is $\geq 15,000/\text{mm}^3$. The absolute band count has also been used as a marker of serious bacterial infection. One study evaluated 1009 febrile infants for sepsis and found that the sensitivity of the absolute band count was significantly superior to the total WBC in predicting outcome.³⁴ Another study looked at the absolute band count in infants ≤ 60 days of age with fever (rectal temperature $\geq 38^{\circ}\text{C}$ [$\geq 100.4^{\circ}\text{F}$]) who were at low risk for serious bacterial infection according to the Rochester criteria. The authors found that the absolute band count varied widely from laboratory to laboratory.³⁵ If the absolute band count is to be relied upon, the ED clinician is advised to check the laboratory's definition of segmented neutrophils.

Arterial Blood Gas Measurements

When managing patients with respiratory infections, the ED clinician must decide whether pulse oximetry is sufficient or arterial blood gas measurements are also needed. As previously mentioned, the pulse oximeter has often been labeled the "fifth vital sign," since it is a good indicator of respiratory status. However, readings can be affected by hypoperfusion or cold extremities. Although arterial blood gas measurements cannot discriminate between viral and bacterial infections, they may aid in the detection of hypoxemia in patients with community-acquired pneumonia. In a prospective cohort study of 2267 patients, hypoxemia was most associated with pneumonia in patients older than 30 years of age who had chronic obstructive pulmonary disease (COPD), a respiratory rate greater than 24 breaths/minute, altered mental status, and involvement of more than 1 lobe on chest x-ray.³⁶ The authors concluded that patients meeting these criteria should be considered for arterial blood gas testing on presentation to assess oxygenation status and determine the course of treatment. Arterial blood gas results provide a notably better assessment of the presence of hypercarbia than do venous blood gas results, although venous sampling has been reported to be a good initial screen for patients with respiratory complaints.³⁷ There is also strong evidence that venous and arterial bicarbonate levels correlate in hemodynamically stable patients in diabetic ketoacidosis.^{ix} However, the value of venous blood gas measurements as a true indication of oxygenation and perfusion status has not yet been completely accepted.

Urinalysis

A urinalysis is not necessary to diagnose a urinary tract infection (UTI) in women ages 18 to 65 who present with the typical symptoms of dysuria, frequency, and urgency and who have no complicating factors.³⁸ Such factors include diabetes, pregnancy, immunosuppression, underlying urinary tract disease or renal calculi, a recent medical intervention (hospitalization or catheterization), recurrent UTIs, or failure of therapy. If the ED clinician prefers to evaluate uncomplicated cases by means of urinalysis, a urine culture is not warranted. However, both a urinalysis and a urine culture are recommended in patients with complicating factors and those with pyelonephritis.³⁹ Children diagnosed with UTI may initially have a negative result on urinalysis but positive urine cultures. Therefore, in children, a urine culture should always be obtained and followed up, even if the UTI is treated empirically.⁴⁰

Urinalysis does have its limitations. Although the finding of pyuria on urinalysis has a high sensitivity (95.8%), it is not very specific (71%). The presence of bacteria on microscopic examination is a less sensitive (40% to 70%) but more specific finding (85% to 95%). A positive test for leukocyte esterase and nitrates, however, has a much higher correlation with culture-proven UTI.⁴¹ UTIs caused by gram-positive organisms will not be nitrate-positive.

In many centers, urine dipstick testing has replaced urinalysis because it can be done quickly and is convenient and inexpensive. However, studies have shown that dipsticks do not reliably rule in infection when compared with urine culture results.^{42,43} A review of the literature that included 70 publications concluded that in adults the urine dipstick test alone was reliable in excluding the presence of infection if both the nitrites and leukocyte esterase were negative; however, this test alone was not found to be useful for ruling in infection.⁴⁴

Lumbar Puncture

Examination of the cerebrospinal fluid (CSF) should include a cell count, glucose, protein, culture, and Gram stain on all patients. More specific studies, such as viral cultures, a VDRL test, and cryptococcal antigen should be carried out if clinically indicated.⁴⁵ Currently, many ED clinicians order a head CT in patients with suspected meningitis before proceeding to a lumbar puncture (LP), in order to screen for any intracranial abnormalities that may lead to brain herniation secondary to removing CSF. One study by Hasbun et al found that baseline risk factors for an abnormal head CT included having an age greater than 60 years, immunocompromised status, abnormal level of consciousness, history of central nervous system (CNS) lesion, focal neurologic signs, and history of seizure within 1 week of presentation.⁴⁶ They recommended that patients

with any of these factors undergo a head CT prior to LP to evaluate for any mass effects, which may potentially lead to herniation; patients without these risk factors may undergo LP without prior head CT. Following these recommendations would significantly reduce the number of unnecessary head CTs currently ordered. Once there is a clinical suspicion for meningitis, blood cultures and an LP must be performed immediately, and antibiotic therapy should be started without delay to help prevent adverse outcomes. Blood cultures should be drawn before antibiotics are begun, since 47% to 77% of patients with bacterial meningitis have positive growth on blood cultures.⁴⁷⁻⁴⁹ Once antibiotics are given, an LP should be performed as soon as possible since CSF sterilization can occur rapidly. One retrospective study examined the rate at which parenteral antibiotic pretreatment in a pediatric population sterilizes CSF cultures and found that there was complete sterilization of meningococcus (*Neisseria meningitidis*) within 2 hours and the beginning of sterilization of pneumococcus by 4 hours of therapy.⁵⁰ An adequate culture can help guide antibiotic therapy and may also rule out bacterial meningitis. Clinicians should also attempt to obtain an opening pressure on cooperative patients. A pressure markedly elevated from the normal pressure of 50 to 180 H₂O may indicate significant intracranial pathology, and if significantly elevated, only the smallest sample possible for the required testing should be removed. Obtaining an elevated opening pressure may also permit treatment prior to the identification of the etiology.^x

Acute Phase Reactants

The acute phase reactants are proteins produced by hepatocytes and other cell types in response to infection, inflammation, and tissue injury. These reactants are fairly nonspecific and not sensitive enough to identify individual disease entities.

C-reactive protein (CRP) concentrations increase with acute invasive infections, which parallel the severity of the inflammation or tissue injury.⁵¹ However, the CRP is an expensive test that may not be available at all institutions. Currently, the only disease entities studied in the context of evaluating the usefulness of CRP and erythrocyte sedimentation rate (ESR) in the ED setting are pelvic inflammatory disease (PID), appendicitis, and septic arthritis. The ESR may help distinguish between PID and unruptured appendicitis. In 1 study, only 10% of patients (2 out of 20) with unruptured appendicitis had an elevated ESR (> 20 mm/h) in contrast to 80% of patients with PID; in the same study, 67% of patients with ruptured appendicitis had an ESR above 20 mm/h.⁵²

The ESR may also be helpful in narrowing the differential diagnosis of a limping child. The 2 primary diagnostic candidates are septic arthritis and toxic

synovitis. If the ESR is elevated (> 25 mm/h), patients may be at higher risk for septic arthritis. In recent years, CRP has gained in popularity in conjunction with ESR as a diagnostic tool. In a study involving 265 children from 3 months to 15 years of age, 98% of patients had an elevated ESR (> 20 mm/hr) and/or CRP (> 20 mg/L).^{xi} Our recommendation, no matter what the laboratory results indicate, is joint aspiration and culture if there are positive clinical findings in patients at high risk. However, in patients at low risk who have unremarkable levels of ESR and CRP, close observation is probably warranted. Measuring ESR may also be useful in monitoring the pathologic process, since the ESR level normalizes at a faster rate (eg, in 10 days vs 21 days for CRP during treatment in septic arthritis).^{xi}

Another acute phase reactant currently under investigation is serum procalcitonin (PCT). This aminopeptide is identical to the precursor of calcitonin, but it has no hormonal activity. PCT is usually found only in the thyroid gland, but in cases of bacterial infection it can be found in serum.⁵³ The attractiveness of PCT lies in its response to both infection and inflammation, thus reflecting both microbiologic findings and the host response, which significantly influence prognosis and outcome. In addition, it has a theoretical advantage over bacterial culture owing to its expedience. The downside is that PCT, like CRP, is an indirect marker of infection. One study has shown that PCT levels are significantly increased in cases of severe bacterial infection and sepsis,⁵⁴ whereas they are low in viral infections and localized inflammatory reactions. Another study suggests that levels of PCT and CRP relate to the severity of organ dysfunction in patients with sepsis and in those with other disorders, but concentrations are still independently higher during infection. One meta-analysis has concluded that PCT represents a good biologic marker for sepsis, severe sepsis, or septic shock, all of which are difficult to diagnose in critically ill patients.^{xii}

Further study of this reactant is clearly warranted,⁵⁵ including whether a determination of PCT levels would change the management protocols in patients meeting the systemic inflammatory response syndrome (SIRS) or sepsis criteria.

Radiographic Studies

When performing radiologic studies in the ED, the ED clinicians must judiciously choose the modality that offers the highest yield. For example, Waters view x-rays to diagnose sinusitis are only 68% sensitive and 87% specific for maxillary sinusitis. Therefore, if a radiographic study is needed, a high-resolution CT scan is preferred.⁵⁶ ED clinicians should also beware that in certain populations, such as the very young, a present pathology like bacterial pneumonia may not translate to a positive chest x-ray.^{xiii}

Gram Stain And Culture

In a few instances, the Gram stain can be useful, mainly to identify bacteria in those body fluids that are normally sterile.⁸ In the ED setting, that usually means either the CSF, urine, or abscesses. An India ink preparation is indicated when cryptococcal meningitis is suspected. A Gram stain for ascitic fluid may also be done, but its yield is extremely low in patients suspected of having spontaneous bacterial peritonitis.^{xiv}

Sputum Gram staining is generally not useful and is not recommended in community-acquired pneumonia (CAP) because it is difficult to obtain an adequate specimen and the criteria that describe a positive smear are variable.⁵⁷ In addition, this test does not identify the atypical organisms usually implicated in community-acquired pneumonia.⁵⁸

Nevertheless, a good-quality sputum sample can still help guide antibiotic therapy during a patient's hospital stay for CAP. Several independent studies have demonstrated that Gram stains of patients who have not received previous antibiotic therapy are highly specific in the diagnosis of pneumococcal and *H influenzae* pneumonia.^{xv,xvi} One caveat, however: in these studies, the sputum samples that were considered "good" represented only 60% to 70% of the total number of samples obtained. Because it may take time to obtain and process a sputum sample (and national guidelines now "benchmark" time-to-treatment for patients with CAP) Gram staining is usually not used to guide initial management. Still, results of this test may be useful for overall in-hospital management.

Sputum cultures may also be helpful for ED clinicians on patient return visits to the ED or for follow-up with the patient's primary care physician.⁵⁹

Throat Cultures

There is some controversy around when to prescribe antibiotics for pharyngitis, as well as when to obtain throat cultures or perform a rapid antigen detection test (RADT) for strep. In 2002, the Infectious Diseases Society of America (IDSA) issued a practice guideline for the diagnosis and management of group A streptococcal pharyngitis.⁶⁰ They recommend that if the clinical suspicion for strep throat is low — based on the absence of fever, anterior cervical adenopathy, and palatal petechiae — symptomatic treatment is all that is required. Symptoms such as coryza, absence of fever, diarrhea, and conjunctivitis point to a viral etiology. If there is suspicion for group A strep, either throat culture or RADT is in order; however, because RADT is often significantly less sensitive than the culture; the IDSA recommends that a negative result on RADT be followed with a throat culture in adolescents and children. Testing should be conducted in children who have had contact with persons confirmed to have had strep throat in the preceding 2 weeks. Children should not be treated for group A

streptococcal pharyngitis in the absence of a positive test. For adults, the IDSA does not suggest confirmation of a negative RADT, because the risk of sequelae of untreated strep throat, such as rheumatic fever and streptococcal infection, are very low.⁶⁰ Currently, the recommendation specifically for the ED clinician is that "rapid strep tests should be a logical part of management of some ED patients, and culture confirmation of negatives is still advisable."⁶¹ ED clinicians should be aware that the current streptococcal guidelines are being reevaluated and are expected to be available in the spring of 2010.

Blood Cultures

The identity of an infectious organism usually cannot be known with certainty in the ED, since it can be a few days before culture results are available. Blood cultures should be performed in patients at increased risk for complications, such as those who have sickle cell disease or are immunosuppressed (eg, because of HIV or malignancy), steroid-dependent, or admitted from a nursing home. Obviously, blood cultures should be drawn in patients who may have sepsis or infective endocarditis or bacterial meningitis. The most recent guidelines from the IDSA, published in 2007, recommend blood cultures for patients with CAP but only in certain circumstances and under certain conditions, including intensive care unit admission, cavitary lung lesions, leukopenia, active alcohol use, chronic or severe liver disease, asplenia, positive result for pneumococcal urinary antigen, and pleural effusion.^{xvii} (Note that these guidelines differ from the previous recommendation, from 2000.^{62,63})

These guidelines also recommend obtaining blood cultures in patients with diabetic foot infection and patients with infectious diarrhea, but only when bacteremia or systemic infection is suspected.^{64,65} ^{xviii} On the other hand, the guidelines advise against obtaining blood cultures in patients with complicated intra-abdominal infections such as those due to bowel injuries, acute perforations, acute cholecystitis, and appendicitis, since the results would not provide any additional clinically relevant information.⁶⁶

Some studies suggest that routine blood cultures are not helpful and incur unnecessary expense in patients who are admitted with community-acquired cellulitis, pyelonephritis, or pneumonia who lack the risk factors described above.⁶⁷⁻⁷⁰ Specifically, 2 separate studies showed that positive blood cultures in pyelonephritis in most cases were either resulted from a contaminant or grew the same organism found on the urine culture.^{71,72} In both of these studies, antibiotic therapy was not changed in response to the blood culture results. Although the findings in some studies that have assessed the usefulness of blood cultures conflict with the IDSA guidelines, ED clinicians are still encouraged to follow the guideline's major recommendations.

Treatment Of Bacterial Infections

When choosing an antibiotic, think in terms of “the bug, the drug, and the host,” since each of these components strongly influences the choice of therapy. We must select the right weapon (the drug) to defeat the enemy (the bug) and save our patient (the host), with the least possible collateral damage. Thinking along these lines will help us empirically select the right medications for any given infection.

The Internet may provide useful information for determining the treatment strategy for choosing the appropriate antibiotics and dosage. Uptodate (www.uptodate.com), a site well known to most practitioners, offers the general principles of disease diagnosis and management. However, the annual subscription fee and the time required to read a certain topic may be prohibitive for clinicians. For specific information about a specific disease etiology or an antibiotic, the Hopkins Antibiotics Guide (<http://hopkins-abxguide.org/>) offers easy-to-access information free of charge. The site requires a quick registration, but then offers information, including the approximate cost of the medication, in an easy-to-access format, which is perfect for the busy ED clinician.

Some other online sites to consider include a prescription price checker at www.drugstore.com if cost of a certain medication is an issue. The same site also allows clinicians to obtain the exact name of a medication a patient may have been using prior to arrival in the ED (http://www.drugs.com/pill_identification.html). For pediatric weight-based antibiotics, practitioners may consider using Med-Calc (<http://www.medcalc.com/pedidose.html>) for calculations of the exact dosage and concentration.

Narrow-Versus Broad-Spectrum Antibiotics

First and foremost, the drug we select (our “weapon”) must target and kill the organism responsible for the infection. We try to deduce the identity of the most likely bug by following the various diagnostic approaches described previously, taking into account all the possible offenders. Then we choose between 2 types of weapons: “elephant guns” (ie, broad-spectrum antibiotics, which are nonspecific) and “rabbit guns” (ie, narrow-spectrum antibiotics, which are aimed at specific bacteria).

Usually, elephant guns are not necessary to kill a rabbit — meaning that a narrow-spectrum antibiotic, when used appropriately, will be just as effective as a broad-spectrum one but will not lead to undue resistance among the host’s bacterial flora. The emergence of resistant strains of bacteria that were not originally targeted by the drug is an increasingly problematic side effect of employing the so-called “big guns.”^{17-21,23,73} This is not to say that broad-

spectrum antibiotics have no place in the treatment of very ill patients, such as in cases where you cannot afford to miss even 1 potential enemy without the risk of losing the war. Broad-spectrum antibiotics can and should be used for infections with multiple etiologic agents, such as chronic diabetic foot infections or peritonitis, or for patients with infections at multiple sites.

Combining Antibiotics

Combining different antibiotics is another means of broadening coverage.⁹ This may be done for several reasons. One reason is to cover infections that may be caused by multiple organisms, eg, pelvic inflammatory disease (PID), in which *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, anaerobes, and gram-negative bacteria are often found together on culture. To defeat all the offenders in this situation, combination therapy is indicated: ceftriaxone with doxycycline for outpatient management and IV cefotetan with doxycycline in hospitalized patients. Another reason for combining antibiotics is to cover simultaneous infections at multiple sites, as in the nursing home patient who has pneumonia, a UTI, and infected decubiti.

Combination therapy also takes advantage of the synergy that exists between certain antibiotics, enhancing their individual actions when they are used together, particularly against highly virulent organisms. An example would be combining penicillin with aminoglycosides to treat enterococcal endocarditis. Yet another reason for using combination therapy is to treat critical patients in whom the source of infection is unknown. Remember, however, it is important to use combination therapy only when necessary, since it has the potential to increase side effects and is more expensive than monotherapy.

Routes Of Administration

In addition to choosing the most appropriate antibiotic(s), the ED clinician must also determine the proper delivery method. Depending on how ill the patient is, high concentrations of the drug(s) in serum or tissue may be needed rapidly, requiring the IV rather than the oral route, such as in sepsis or meningitis. At certain sites of infection, such as the central nervous system or heart, higher concentrations of the drug are likely to be more effective; thus, IV therapy is preferable. For patients with only mild infections, the oral route would be preferable because it is more convenient and more cost-effective. It should be noted as well that certain medications, such as levofloxacin and gatifloxacin, have the same bioavailability in both the oral and the IV preparations.

Intertwined with these considerations is the influence of the patient (the “host”) on the choice of drugs. First, the ED clinician must assess how sick the patient is and make choices that correspond to the severity of the disease. The sicker the patient, the

more aggressive the treatment must be. The choice of prescribing an oral regimen on an outpatient basis versus admission for IV therapy will depend on the clinical assessment, the suspected organism, and the patient's comorbidities (eg, parenteral imipenem-cilastatin rather than oral azithromycin for a nursing home patient with sepsis and massive pneumonia).

Patient comfort is also an important consideration. For example, the CDC recommends oral doxycycline for the treatment of PID when possible, since the IV infusion of doxycycline is incredibly painful. The recommendation is true even for patients in the hospital.^{xix}

Toxicity

Another factor to consider in therapeutic decision-making is the toxicity of the antibiotic. Obviously, preventing “collateral damage” by using the least-toxic drug is a major goal of treatment. Toxicity may manifest in many ways. Allergic reactions are common and will obviously limit the choice of antibiotics for some patients. There are also groups of antibiotics known for crossover allergies—penicillins and cephalosporins, for example—although the incidence of these reactions is a matter of controversy. One prospective study of 41 patients concluded that cephalosporins were safe in therapeutic doses if they did not share an identical side chain with the penicillin responsible for the allergic reaction.⁷⁴ Although the risk of hypersensitivity may be increased in penicillin-allergic patients who receive cephalosporin antibiotics, this risk is considered significant only with the first-generation cephalosporins. Crossover allergies between penicillins and carbapenems appear to be more frequent.⁷⁵

The profile of toxicity is an important issue, since some patients are more susceptible than others to a given side effect. For example, nephrotoxic agents, like aminoglycosides, should be avoided in patients with decreased baseline kidney function, and drugs that affect growing bones, such as tetracyclines, should be avoided in pediatric patients. The more well-known adverse reactions are listed in **Table 8**.

The toxicity of a given antibiotic may be enhanced by many factors. For instance, inborn genetic errors in metabolism can give rise to complications—for example, hemolysis after sulfonamides in glucose-6-phosphate dehydrogenase (G6PD) deficiency. Interactions with other medications can lead to unexpected results. One notorious example is the occurrence of torsades des pointes after combining terfenadine with erythromycin. A less dramatic but more frequent example is the interaction of warfarin with certain antibiotics, such as macrolides, fluoroquinolones, cephalosporins, tetracyclines, and high-dose intravenous penicillins, which increases the International Normalized Ratio (INR).

Other than serious or debilitating adverse

effects, there are the “nuisances,” such as gastrointestinal upset, that can limit compliance with the prescribed antibiotic regimen.⁷⁶ Erythromycin is infamous for its gastrointestinal side effects, seemingly making the cure worse than the disease. Although erythromycin is a very effective and inexpensive drug for treating respiratory tract infections, its side effects have been shown to adversely affect patient compliance.⁷⁷

Indications For Treatment

Antibiotics are clearly indicated when lobar pneumonia is confirmed by chest x-ray, a UTI is confirmed by urinalysis, or meningitis is suspected. However, other infections are often treated with antibiotics even though they do not necessarily require them. Viruses cause most cases of rhinosinusitis, and bacterial and viral rhinosinusitis are difficult to differentiate clinically. Antibiotics should be reserved for presentations that are more consistent with a bacterial etiology; specifically, for patients whose symptoms last for 7 days or longer and who have maxillary pain or tenderness in the face or teeth (especially if it is unilateral) and purulent nasal secretions.^{78,79}

Uncomplicated acute bronchitis is a respiratory infection in which a cough, with or without phlegm, is the predominant feature in an otherwise healthy adult. In the vast majority of cases, the cause is nonbacterial. Specific viruses associated with acute bronchitis include those that cause lower respiratory tract disease (influenza B, influenza A, parainfluenza type 3, respiratory syncytial virus) and those that cause upper respiratory tract disease (coronavirus, adenovirus, rhinovirus). Only *Bordetella pertussis*, *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae* (TWAR) have been established as nonviral causes (in 10% to 20% of cases) of uncomplicated acute bronchitis in adults. Patients with uncomplicated acute bronchitis should not be treated with antibiotics.^{80,81}

Viruses cause most cases of pharyngitis. Pharyngitis caused by group A beta-hemolytic streptococcus (GABHS) is predominantly a disease of children 5 to 15 years of age. Its prevalence is approximately 30% in children diagnosed with pharyngitis but only 5% to 15% in adults with this diagnosis. Patients should be screened for the presence of the 4 criteria: history of fever, tonsillar exudates, no cough, and tender anterior cervical lymph nodes. Patients who meet none or only 1 of these criteria should not be treated with antibiotics. Patients meeting 2 or 3 of the criteria should be tested using RADT and treated with antibiotics if the result is positive. Patients who meet all 4 criteria should be treated without the need for testing.^{82,83}

The most common bacterial causes of otitis media include *Streptococcus pneumoniae* (25% to 50%), nontypable *H influenzae* (15% to 30%), and *Moraxella catarrhalis* (3% to 20%). Viruses such as respiratory syn-

Table 8. Antibiotics Of Choice, By Pathology**Pharyngitis¹²⁴⁻¹²⁷**

First Choice	Second Choice
PCN VK 500 mg PO BID x 10 days*	Erythromycin base 500 mg QID x 10 days [†]
Benzathine penicillin G 1.2 million units IM x 1	1st- or 2nd-generation cephalosporin: Cefuroxime axetil 250 mg BID x 4 days Cefpodoxime proxetil 100 mg BID Cefdinir 300 mg q 12 hour x 5-10 days Cefprozil 500 mg QD x 10 days Clindamycin 300 mg PO TID x 10 days [‡]

*Amoxicillin is used in young children because of better taste.

[†]Other macrolides can be used as well, though the price may be prohibitive.

[‡]Mostly for patients with repeated episodes of pharyngitis.

Otitis Media^{*118,128-130}

First Choice	Second Choice
Amoxicillin 80-90 mg/kg/d div q12 or q8 Duration of treatment: < 2 years old x10 days; > 2 yrs old x 5-7 days	Amoxicillin/clavulanic acid 90 mg/kg/d div BID [†] Oral 2nd- or 3rd-generation cephalosporin [†] : Cefuroxime axetil 30 mg/kg/d div q12 Ceftriaxone 50 mg/kg IM x 1, followed by oral regimen Trimethoprim/sulfamethoxazole 8 mg/kg/d div BID [§] Macrolide [§] : Clarithromycin 15 mg/kg/d div q12h Azithromycin 10 mg/kg/d on day 1, then 5 mg/kg/d on days 2-5 or 30 mg/kg x 1 dose

*Children at low risk for complications may not require antibiotic treatment. This group consists of patients with mild symptoms who are older than 2 years, are not attending day care, and have not received antibiotics within the prior 3 months.

[†]Children with high fever, ill-appearing, and patients with prior treatment failure.

[§]High percentage of pneumococcus is resistant.

Acute Exacerbation of Chronic Bronchitis^{*104,118}

First Choice	Second Choice
Macrolide: Azithromycin 500 mg PO initial dose then 250 mg PO QD x 4 days	Tetracyclines [§] : Doxycycline 100 mg PO BID
Fluoroquinolone [†] : Levofloxacin 500 mg PO QD Gatifloxacin 400 mg PO QD	2nd- or 3rd-generation cephalosporin [†] : Cefaclor 500 mg q8h Cefixime 400 mg PO QD Cefpodoxime proxetil 200 mg PO q12 Cefprozil 500 mg PO q12
Amoxicillin/clavulanic acid 875/125 mg PO BID or 500/125 mg PO TID [‡]	Trimethoprim/sulfamethoxazole: DS 1 tab (160 mg TMP) PO BID [§]

*Antibiotic therapy controversial; uncomplicated bronchitis is usually not treated in patients without COPD.

[†]Extended-spectrum.

[‡]Does not cover atypicals.

[§]Pneumococcus increasingly resistant

Table 8. Antibiotics Of Choice, By Pathology (Continued)**Community-Acquired Pneumonia^{118,131-134}**

	First Choice	Second Choice
Ambulatory patients*	Macrolide [†] : Azithromycin 500 mg PO QD X 1 then 250 mg PO QD Clarithromycin 500 mg PO BID Tetracyclines [†] : doxycycline 100 mg PO BID Fluoroquinolone [§] : Gatifloxacin 400 mg PO QD	Amoxicillin/clavulanic acid 875/125 mg PO BID [†] 2nd-generation cephalosporin [†] : Cefdinir 300 mg PO q 12 Cefpodoxime proxetil 200 mg PO q12 Cefprozil 500 mg PO q12 cefuroxime axetil 250-500 mg PO q 12
Ambulatory patients > 60 years old[§]	Fluoroquinolone [§] : Levofloxacin 500 mg PO QD Gatifloxacin 400 mg PO QD	Amoxicillin/clavulanic acid 875/125 mg PO BID [†]
Hospitalized patients	Cefotaxime 2.0 gm IV q4 - q8 +/- macrolide [¶] Beta-lactam/beta-lactamase inhibitor +/- macrolide [¶] Fluoroquinolone: Levofloxacin 500 mg IV QD Gatifloxacin 400 mg IV QD	Cefuroxime +/- macrolide Azithromycin ^{¶¶¶}

*Course of treatment until patient is afebrile, usually 3-5 days, may require 7-10 days.

[†]*S pneumoniae* increasingly resistant.

[‡]Does not cover atypicals.

[§]Extended-spectrum

[♦]Broad-spectrum antibiotics with low incidence of resistance suggested if sending these patients home.

^{¶¶}Vancomycin can be added in ill patients requiring ICU admission.

[#]Metronidazole or clindamycin should be added if aspiration is suspected.

^{**}IV

Urethritis/Cervicitis^{*10,135-139}

First Choice	Second Choice
Azithromycin 1 gm PO x 1 dose + ceftriaxone 125 mg IM x 1 dose	Ofloxacin 400 mg PO x 1 dose then 300 mg PO q12 x 7 days [†]
Doxycycline 100 mg PO BID x 7 days [†] + ceftriaxone 125 mg IM x 1 dose [†]	Erythromycin base 500 mg PO QID x 7 days + cefixime 400 mg PO x 1 dose or ceftriaxone 125 mg IM x 1 dose [†]
Azithromycin 1 gm PO x 1 dose + cefixime 400 mg PO x 1 dose or ciprofloxacin 500 mg PO x 1 dose [†]	Ciprofloxacin 500 mg PO x 1 dose [†] + azithromycin 1 gm PO x 1 dose or tetracyclines ^{†§} or erythromycin [§]
Amoxicillin [‡] + ceftriaxone 125 mg IM x 1 dose or cefixime 400 mg PO x 1 dose	

*Caused by *N gonorrhoeae* or *C trachomatis*; patients should have a test for syphilis performed.

[†]Contraindicated in pregnancy.

[‡]Treatment of chlamydia in pregnancy.

[§]7-day regimen.

Table 8. Antibiotics Of Choice, By Pathology (Continued)

Pelvic Inflammatory Disease^{135,139}

	First Choice	Second Choice
Outpatients*	Ofloxacin 400 mg PO BID Levofloxacin 400 mg PO qd + metronidazole 500 mg PO BID Ceftriaxone 125 mg IM/IV x 1 dose + doxycycline 100 mg PO BID x 14 days [†]	Azithromycin [‡]
Hospitalized patients	Cefotetan 2 gm IV q12 or cefoxitin 2 gm IV q12 + doxycycline 100 mg IV/PO q12 Clindamycin 900 mg IV q8 + gentamicin 2 mg/kg IV loading dose then 1.5 mg/kg IV q8h, or 4.5 mg/kg x 1 dose, then doxycycline 100 mg PO BID x 14 days [§]	Ofloxacin 400 mg IV q12 + metronidazole 500 mg IV q8 Ampicillin/sulbactam 3 gm IV q6 + doxycycline 100 mg IV/PO q12 Ciprofloxacin 200 mg IV q12 + doxycycline 100 mg IV/PO q12 + metronidazole 500 mg IV q8 Azithromycin [♦] + metronidazole

*Temp < 38°C (100°F), WBC < 11,000/mm³, minimal evidence of peritonitis, active bowel sounds, able to tolerate oral nourishment.

[†]May add metronidazole if anaerobes strongly suspected.

[‡]1st dose IV, followed by 6-day oral regimen. Consider adding oral metronidazole.

[§]Followed by oral doxycycline.

[♦]IV.

Intra-Abdominal Infections And Peritonitis^{8,10,118}

First Choice	Second Choice
Beta-lactam/beta-lactamase inhibitor +/- aminoglycoside*: Ampicillin/sulbactam 3 gm IV q6 Piperacillin/tazobactam 3.375 gm IV q6 Ticarcillin/clavulanate 3.1 gm IV	Fluoroquinolone + metronidazole or clindamycin: ciprofloxacin 500 mg IV q6 + metronidazole 500 mg IV q6
Cefotetan 2 gm IV q12 or cefoxitin 2 gm IV q 8h +/- aminoglycoside*	Carbapenem +/- aminoglycoside:* Imipenim/cilastin 500 mg IV q6 or meropenem IV q8 +/- aminoglycoside
3rd-generation cephalosporin + metronidazole or clindamycin +/- aminoglycoside*	

*Used less frequently as more drugs with gram (-) coverage available, mostly in very sick patients.

Endocarditis^{*8,10,118}

	First Choice	Second Choice
Native Valves IVDU	Nafcillin or oxacillin 2.0 gm IV q4 + gentamicin 1.0 mg/kg IM/IV q8	Vancomycin 15 mg/kg IV q12
Non-IVDU	Penicillin G 20 mu IV QD or ampicillin 12 gm IV QD + nafcillin or oxacillin 2.0 gm IV q4 + gentamicin 1.0 mg/kg IM/IV q8	Vancomycin 15 mg/kg IV q12 + gentamicin 1.0 mg/kg IM/IV q8
Prosthetic Valves	Vancomycin 15 mg/kg IV q12 + gentamicin 1.0 mg/kg IM/IV q8+ rifampin 600 mg PO QD	

*Empiric treatment before culture results available.

Abbreviations: IVDU, intravenous drug user.

Table 8. Antibiotics Of Choice, By Pathology (Continued)

Cellulitis^{8,10,118}		
	First Choice	Second Choice
Outpatients	Dicloxacillin 500 mg PO q6 Amoxicillin/clavulanic acid 500 mg PO TID*	Macrolide: Azithromycin 500 mg PO initial dose then 250 mg PO QD x 4 days 1st-generation cephalosporin: cephalexin 500 mg PO QID x 7-10 days
Hospitalized Patients	Nafcillin or oxacillin 2.0 gm IV q4 Carbapenem†: Imipenem/Cilastin 0.5 gm IV q6 Meropenem 1.0 gm IV q8 Beta-lactam/beta-lactamase inhibitor†	Macrolide IV 1st-generation cephalosporin IV Fluoroquinolone + clindamycin or metronidazole†
Bite Wounds		
Mild	Amoxicillin/clavulanic acid 500 mg PO TID*	Fluoroquinolone + clindamycin or trimethoprim/sulfamethoxazole
Severe	Ticarcillin/clavulanate 3.1 gm IV q6 Ampicillin-sulbactam 3.0 gm IV q6	Fluoroquinolone + clindamycin or trimethoprim/sulfamethoxazole
Diabetic Foot		
Mild infection previously untreated	1st-generation cephalosporin: cephalexin 500 mg PO QID x 14 days Clindamycin: 300 mg PO qid or 450-900 mg IV q8	Amoxicillin/clavulanic acid 875/125 mg PO q12 or 500/125 mg q8
Severe‡	Beta-lactam/beta-lactamase inhibitor: Ampicillin/sulbactam 3.0 gm IV q6 Piperacillin/tazobactam 3.375 gm IV q6 or 4.5 gm IV q8 Cefoxitin or cefotetan Fluoroquinolone + clindamycin or metronidazole	Carbapenem: Imipenem Cilastin 0.5 gm IV q6 meropenem 1.0 gm IV q8 Nafcillin or oxacillin 2.0 gm IV q4 + gentamicin 1.0 mg/kg IM/IV q8 + metronidazole 500 mg IV q6

*Bite wounds.

†Skin infection with sepsis.

‡Extensive involvement or failed prior treatment.

Table 8. Antibiotics Of Choice, By Pathology (Continued)

Meningitis^{10,118}		
	First Choice	Second Choice
Newborns	Ampicillin + cefotaxime (dosage varies by age of patient and weight)	Ampicillin + gentamicin
Patients 2 Months-60 Years	Ceftriaxone 2 gm IV q12 or cefotaxime 2.0 gm IV q4-6 +/- vancomycin 500-750 mg IV q8* +/- rifampin* Peds: Ceftriaxone 80-100 mg/kg div dose q12-24 +/- vancomycin 15 mg/kg IV q6	Meropenem [†] 1.0 gm IV q8+ /-vancomycin 500-750 mg IV q8* Peds: Meropenem 40 mg/kg IV q8 + vancomycin 15 mg/kg IV q6
Patients older than 60 or immune-compromised	Ceftriaxone 2.0 gm IV q12 or cefotaxime 2.0 gm IV q6 +/- vancomycin* + ampicillin 2.0 gm IV q4 [†] +/- gentamicin [†]	Meropenem 1.0 gm IV q8 +/- vancomycin*
Penicillin-allergic patients[‡]	Chloramphenicol 50 mg/kg up to 1.0 gm IV q6 + vancomycin 500-750 mg IV q6 +/- rifampin* + trimethoprim Sulfamethoxazole 15-20 mg/kg/day div q6-8 [§]	Aztreonam [♦] + vancomycin + trimethoprim/sulfamethoxazole [§]

*Depending on the prevalence of resistant strains.

[†]Add-on to other antibiotics for *Listeria* coverage.

[‡]Cefotaxime and ceftriaxone may still be safe to use.

[§]Covers *Listeria*.

[♦]Gram (-) coverage. In children > 1 mo of age, highly recommended to give dexamethasone 0.4 mg/kg q12 IV x 2 days. Give with or just before 1st dose of antibiotic to block TNF.

[¶]May not be used in penicillin-allergic patients.

Table 8. Antibiotics Of Choice, By Pathology (Continued)

UTI^{10,18,142}

<p>Uncomplicated Infection (Cystitis) Usual duration of treatment is 3 days</p>	<p>Trimethoprim/sulfamethoxazole: 1 tab DS (160 mg TMP) PO BID x 3 days[†]</p> <p>Fluoroquinolone[‡]: Ciprofloxacin 500 mg PO BID Levofloxacin 250 mg PO QD Gatifloxacin 200 or 400 mg PO QD x 3 days</p> <p>1st-generation cephalosporin[‡]: Cephalexin 500 mg PO QID</p> <p>Nitrofurantoin 100 mg PO QID x 7 days[‡]</p>
<p>Pyelonephritis Outpatients</p>	<p>Fluoroquinolone^{‡§}: Ciprofloxacin 500 mg PO BID Levofloxacin 250 mg PO QD Gatifloxacin 200 or 400 mg PO QD x 7 days</p> <p>Cephalosporin[‡]: Cephalexin 500 mg PO QID x 14 days</p> <p>Amoxicillin/clavulanic acid 875/125 mg PO q12 or 500/125 mg PO q8 x 14 days[♦]</p> <p>Trimethoprim/sulfamethoxazole^{†♦}</p>
<p>Hospitalized Patients[#]</p>	<p>Fluoroquinolone[‡]: Levofloxacin 500 mg IV QD Gatifloxacin 400 mg IV QD</p> <p>Ampicillin/sulbactam 3.0 gm IV q6 + gentamicin[*]</p> <p>Beta-lactam/beta-lactamase inhibitor[¶]: Ticarcillin/clavulanate 3.1 gm IV q6 Piperacillin/tazobactam 3.375 gm q6 or 4.5 gm q8 IV</p> <p>Carbapenem^{**}: Imipenem 0.5 gm IV q6 Meropenem 1.0 gm IV q8</p>

*Not in pregnancy.

[†]*E coli* increasingly resistant.

[‡]In pregnancy, 7-10 day course.

[§]7-10-day regimen.

[♦]14 days.

[¶]May need to add aminoglycoside, especially in septic patients.

[#]In septic patients.

Table 8. Antibiotics Of Choice, By Pathology (Continued)

UTI in Children < 6 Years*¹⁴²	
< 2 weeks	Ampicillin + gentamicin [†]
2 weeks to 2 months	Ampicillin + cefotaxime [†]
> 2 months	
Hospitalized	Cefotaxime [†] Ceftriaxone [†] DOSAGES VARY BY WEIGHT AND AGE OF CHILD
Oral regimens[§]	Trimethoprim/sulfamethoxazole Cephalexin Cefixime Nitrofurantoin [♦]

*Empiric treatment pending cultures.

[†]IV therapy until afebrile for 24 hours.

[‡]Can also be used as IM therapy.

[§]For use in older children with mild symptoms, or to complete therapy when IV treatment discontinued.

[♦]For use in older children with mild symptoms.

Sepsis Syndrome^{8,10,118}

	First Choice	Second Choice
Neonates	Ampicillin 25 mg/kg IV q8 + cefotaxime 50 mg/kg q12	Ampicillin 25 mg/kg + ceftriaxone 50 mg/kg IV q24 IV/IM Ampicillin 25 mg/kg + gentamicin or tobramycin 2.5 mg/kg IV q12
Children	3rd-generation cephalosporin: Cefotaxime 50 mg/kg IV q8 Ceftriaxone 100 mg/kg q24 Cefuroxime 50 mg/kg IV q8	
Adults	3rd- or 4th-generation cephalosporin [†] : Cefotaxime 2.0 gm IV q4-8 Ceftizoxime 2.0 gm IV q4 Cefepime 2.0 gm IV q12 Beta-lactam/beta lactamase inhibitor: Piperacillin/tazobactam 3.375 gm IV q4 Ticarcillin/clavulanate 3.1 gm IV q4	Carbapenem: Imipenem/cilastin 0.5 gm IV q6 meropenem 1.0 gm IV q8 Vancomycin 1.0 gm IV q12+ aminoglycoside [‡] Aztreonam 2 gm q6 [§]
Neutropenic (Absolute neutrophil count < 500/mm³)	Beta-lactam/beta lactamase inhibitor: Piperacillin/tazobactam 3.375 gm IV q4 Ticarcillin/clavulanate 3.1 gm IV q4 + Aminoglycoside: Gentamicin 2.0 mg/kg IV q8 Tobramycin 2.0 mg/kg IV q8 Amikacin 15 mg/kg IV q8 +/- Vancomycin 1.0 gm IV q12 [♦]	Carbapenem: Imipenem/cilastin 0.5 gm IV q6, +/- vancomycin 1.0 gm IV q12 [♦] 3rd- or 4th-generation cephalosporin: Cefotaxime 2.0 gm IV q4-8 + vancomycin 1.0 gm IV q12 Cefepime 2.0 gm IV q12, +/- vancomycin 1.0 gm IV q12 [♦] In penicillin-allergic: Vancomycin 1.0 gm IV q12 + aminoglycoside +/- metronidazole 15 mg/kg IV then 7.5 mg/kg IV q6

*When source is unknown, the choice of treatment should be based on the most likely source of infection.

[†]Cefotaxime and ceftriaxone are weak against *Pseudomonas*; ceftazidime should not be used against gram (+).

[‡]Use when MRSA is likely; if also suspecting anaerobes, need metronidazole or clindamycin.

[§]For gram (-) sepsis only.

[♦]If MRSA or indwelling catheter.

cytial virus, rhinovirus, coronavirus, parainfluenza virus, adenovirus, and enterovirus have been found in respiratory secretions and/or middle-ear effusions in 40% to 75% of cases of acute otitis media, which may account for the many “failures” of antibiotic treatment.⁸⁴ There is debate over both the diagnostic criteria and the use and duration of antibiotic therapy for patients with otitis media. Prescribing antibiotics continues to be standard practice in the US, whereas in other parts of the world treatment is given only if symptoms do not resolve in 2 to 3 days.⁸⁵ Approximately 30% or more of each of these organisms are resistant to amoxicillin. Refractory infection, defined as persistence of symptoms and signs for 48 hours after treatment was begun, is an indication to change to a broader-spectrum antibiotic.⁸⁶

Many cases of infectious diarrhea are mild, resolve with supportive care alone, and do not require antibiotic treatment.⁸⁷ When the ED clinician suspects food-borne illness, the differential diagnosis should include viruses (most commonly rotavirus), bacteria, parasites, and noninfectious causes. The initial approach to a patient with a diarrheal illness should include rehydration. Consideration of antimicrobial therapy should be reserved for patients with severe illness (fever, bloody stools), those who experienced onset within the past 48 hours, the elderly, the immunocompromised, and infants.⁸⁸ Also, a history of recent antibiotic use should be obtained, since it predisposes to infection with *C difficile*; in such cases a fecal specimen should be tested for *C difficile* toxin.⁸⁹

The ED clinician should also inquire about recent travel history, since less-common infectious etiologies and treatment strategies might need to be considered.

Bacterial Resistance

Of increasing importance in the management of infectious diseases is the emergence of resistant strains of bacteria. The patterns of resistance in a given community are generally monitored by the local hospital laboratory, which periodically generates summary tables of bacterial susceptibility. In more seriously ill or hospitalized patients with acute infection, the ED clinician should be aware of the resistant organisms when choosing the initial coverage in the ED. For example, in patients with meningitis, it is now recommended^{xx} that vancomycin be included if there is sepsis and highly resistant pneumococcus is present. The initial coverage can always be modified once the organism and its sensitivities are known. Similarly, coverage for pneumonia in patients who qualify for ICU admission would be different from that for stable patients who are admitted to the general medicine ward.

Keep in mind that recommendations for treatment change as bacteria evolve and develop resistance and as new antibiotics are introduced. One recent example is in the treatment of UTI. For

many years the first choice was trimethoprim/sulfamethoxazole, which is now being replaced by the fluoroquinolones, since in many communities the most common pathogen, *E coli*, has become increasingly resistant.⁹⁰ Once again, ED clinicians are encouraged to provide antibiotic therapy based on the bacterial flora and sensitivities specific to the community and institution. Resistance rates above 15% to 20% warrant a change in antibiotic class.^{xxi}

There has been an alarming rise in the number of pathogens that have become resistant to antimicrobial drugs. As a result, it is incumbent upon ED clinicians to understand how this resistance has altered therapeutic guidelines and to prescribe antibiotics only when such treatment is clearly indicated, thus preserving the sensitivity of specific bacteria.^{xxii}

Immunotherapy In Sepsis

Research over the last several decades has shown that inflammatory markers may have a significant role in the pathophysiology of sepsis and septic shock. As a result, several immunotherapies to limit the expression of cytokines have been studied, including interleukins and tumor necrosis factor (TNF). However, most studies have shown either increase in mortality or no change versus placebo.⁹¹ For example, treatments manipulating the TNF receptor and nitrous oxide synthase inhibition at the molecular level have both resulted in increased mortality.^{92,93} Currently, the only FDA-approved agent for severe septic shock is recombinant protein C, and it is only approved for those patients with severe septic shock (APACHE II score > 25). This medication is extremely expensive and has been associated with a significant increase in bleeding risk.⁹⁴ It should be noted that recombinant protein C is currently recommended only for the intensive care environment and is usually not available for the emergency department.^{xxiii}

Methicillin-Resistant *Staphylococcus Aureus* (MRSA)

MRSA bacteremia is responsible for a significant rise in the cost of care, since hospital stays tend to be much longer for patients with this type of infection. In a study from Johns Hopkins, researchers looked at mortality, length of stay, and hospital charges for patients with MRSA bacteremia versus those with methicillin-sensitive *S aureus* bacteremia. Although mortality was high in both groups (22% and 19%, respectively), the difference was not statistically significant. However, of patients who survived, those with MRSA remained in the hospital for more than 2 days longer and accrued an average of \$6,916 more in hospital costs.⁹⁵

How does all this affect the ED clinician, who in most cases does not have the luxury of knowing the infecting organism? In terms of MRSA, the most common site of infection appears to be the soft

tissue. One recent study attempted to determine the prevalence of MRSA in ED patients who had soft tissue infections. Of 137 patients studied, MRSA was isolated from either the nares or a wound site in 119, and 51% of the wound isolates contained MRSA. Thus, in choosing an antibiotic to treat cellulitis or an abscess, ED clinicians must consider the problems associated with MRSA. All cases of MRSA were susceptible to sulfamethoxazole/trimethoprim, and a high percentage was still susceptible to clindamycin. However, only 56% of MRSA cases were susceptible to levofloxacin. The authors of the article have now changed their prescribing regimen for cellulitis, reasoning that simple beta-lactams, such as cephalexin, may not provide adequate coverage. They now mostly prescribe an oral regimen of trimethoprim/sulfamethoxazole and cephalexin. Because of the risk of pseudomembranous colitis in adults, the authors generally reserve clindamycin for children and for patients with severe allergies to other regimens.⁹⁶

Doxycycline may be used as monotherapy, although resistance to it is reported to occur in approximately 20% of cases. Patients treated with doxycycline should be reevaluated again after 24 to 48 hours to assess its efficacy.^{xxiv}

Unfortunately, community-acquired MRSA continues to be a major issue, with many questions still unresolved. Should we begin to change our customary drug regimens empirically, or should we determine the prevalence of MRSA in our community by culturing all wounds and abscesses? What is the role of contact isolation? Is it even feasible to isolate patients in an already overcrowded ED?⁹⁷ More studies are needed to answer these questions before we can make definitive recommendations regarding the diagnosis and treatment of MRSA.

Overprescribing Or Inappropriate Use Of Antibiotics

Much attention is being paid to the rise of drug-resistant organisms in the United States, yet many ED clinicians continue to prescribe antibiotics for infections that may be viral. One potential reason for this may be the perceived expectation on the part of patients (or in the case of children, their parents) that antibiotics should be and will be prescribed for them. Surveys have shown that some clinicians do prescribe antibiotics, even when they know that these drugs are not indicated for the particular condition.⁹⁸⁻¹⁰⁰ The findings of 1 study suggested that clinicians were more inclined to make an unfounded diagnosis of bronchitis in children and to prescribe antibiotics when they felt that the parents expressed an expectation of a course of antibiotics.⁹⁹ A survey of pediatricians found that approximately one-third either occasionally or more frequently complied with parents' requests for treatment with antibiotics. However, 78% of these pediatricians felt that the single most important program for reducing inap-

propriate oral antibiotic use would involve educating parents — as opposed to concerns over legal liability or practice efficiency.⁹⁸

Regardless of the reasons for overprescription of antibiotics, its effects are real. Of particular concern is the emergence of penicillin-resistant *Streptococcus pneumoniae* (PRSP). *S pneumoniae* is a common cause of many infections, ranging from otitis media and sinusitis to community-acquired pneumonia. PRSP rates are on the rise, too, which puts patients with a “common” infection at risk of developing serious complications.¹⁰¹⁻¹⁰⁴ A nationwide, multicenter surveillance study in 1997 found that the rates of PRSP in the United States had reached 34.6%.¹⁰³ Therefore, ED clinicians should be careful to prescribe and administer antibiotics only when indicated and to get involved in educating patients about the dangers of antibiotic overuse.

An interesting study published in 2002 looked at educational outreach programs involving healthcare workers and parents that were designed to reduce unnecessary prescribing of antimicrobials. The results showed an 11% decline in such prescribing that was attributable to the intervention. This conclusion suggests that educating the community may indeed help reduce unnecessary antimicrobial treatment.^{xxv}

Disposition Criteria And Discharge

Determining which patients can be safely discharged home and which require admission to the hospital is a difficult task. Obviously, the ill-appearing patient who is hypotensive with signs of shock or the one who is hypoxic will need to be admitted. (In fact, very ill patients will need to be admitted to an intensive care setting.) Admission is also indicated for patients with infections that need to be treated with intravenous antibiotics in order to achieve adequate bactericidal levels of these drugs in the serum or tissues. This would be the case, for example, for endocarditis or meningitis.

For some infectious diseases, criteria have been developed to assist the ED clinician in making a disposition. For instance, several organizations have published specific criteria for admitting patients with community-acquired pneumonia. Practice guidelines from the Infectious Diseases Society of America recommend that the decision for hospitalization be based on the prediction rule for short-term mortality derived from the Pneumonia Patient Outcome Research Team (Pneumonia PORT). Patients are stratified into 5 severity classes by means of a 2-step process. In Step 1, Class I patients are those who are under 50 years of age who do not have the following 5 comorbid conditions: neoplastic disease, liver disease, congestive heart failure, cerebrovascular disease, or renal disease, whose vital signs are normal or only mildly abnormal, and whose mental

Cost- And Time-Effective Strategies For Patients Who May Need Antibiotics

1. Prescribe antibiotics for patients only when necessary.

Resist giving in to pressure from the patient to prescribe antibiotics for a viral upper respiratory infection. Take the time to educate patients about the appropriateness of antibiotics and the increasing bacterial resistance to antibiotics.

Risk Management Caveat: Be sure that all patients being sent home have follow-up care with their primary care physicians. Although the patient will have a complete history and physical examination that will decide if they need antibiotics as treatment, occasionally patients will be misdiagnosed. For example, what may seem like a viral pharyngitis on initial presentation may turn out to be strep pharyngitis with development of a peritonsillar abscess.

2. Consider costs of antibiotics.

Always consider the insurance status of the patient and what medications are within their financial means. Frequently, doctors prescribe expensive antibiotics for patients without considering whether they can afford them. This may lead to noncompliance and an illness left untreated, with possible complications in the future. Always consider the cost of the prescribed antibiotic — speak with patients about prescription plan coverage and their ability to pay out of their own pocket, if necessary.

Risk Management Caveat: Do not compromise on necessary bacterial coverage because of cost. If there is no cheaper equivalent for needed coverage, or if the patient cannot afford prescribed antibiotics at all, then consult the social worker for assistance.

3. Consider the bacterial coverage needed by an antibiotic.

Consider the bacterial coverage needed when deciding which antibiotic to prescribe. Avoid prescribing a “big gun” antibiotic if broad-spectrum coverage is not required. Also, when prescribing an antibiotic, consider the patterns of resistance for the community- and hospital-acquired organisms in the area.

Risk Management Caveat: Consider any past failed treatment for the same condition and the antibiotics used. For example, a child presenting with otitis media after 3 days of failed treatment with amoxicillin may now need broader coverage with amoxicillin/clavulanic acid to cover

drug-resistant *Streptococcus pneumoniae*. Also, if a patient is less than 2 years old, attends day care, or has been treated with antibiotics in the preceding 3 months, they may be at high risk for drug-resistant *S pneumoniae* and should be treated initially with high-dose amoxicillin.

4. Limit testing to selected patients.

Often tests are done on a well-appearing patient who is ultimately diagnosed with a benign febrile illness, such as a viral syndrome. Only a small minority of patients with a fever require a CBC, urinalysis, chest x-ray, or urine, throat, or blood cultures, etc. These tests are not only costly but are usually unnecessary to make a diagnosis. They can also be time-consuming, not to mention inconvenient and unpleasant for the patient.

Risk Management Caveat: If tests are deemed clinically necessary, then they should always be performed, regardless of the cost. Also, for tests like blood cultures, the results must be checked and acted on appropriately. If the results are not complete during the ED visit, then appropriate follow-up to check these results must be arranged.

5. Admit patients intelligently.

Obviously, not every patient with an infection needs to be admitted. Decisions to admit patients should be weighed carefully and not just a reflexive response. For example, the American Thoracic Society has developed guidelines for admission for patients with community-acquired pneumonia, and guidelines such as these should be followed whenever possible. Also, special strategies, such as giving intravenous antibiotics by the visiting nurse service, may be an effective cost-cutting strategy that can be considered under some special circumstances.

Risk Management Caveat: Patients should be given the benefit of the doubt. If a patient is at risk for noncompliance, or if close follow-up cannot be assured, then the patient should be admitted. Social problems, such as alcoholism, drug abuse, homelessness, and lack of family support, must be taken into account before discharging the patient. In fact, sometimes it may be more cost-effective to admit a patient early, rather than discharging them only to admit them later, when they return to the ED with a serious complication of their infection that requires costly intensive care.

status is normal. In Step 2, patients not assigned to Class I are stratified into Classes II to V on the basis of points assigned for 3 demographic variables (age, sex, and nursing home residency), 5 comorbid conditions (as listed above), 5 physical examination findings, and 7 laboratory and/or radiographic findings. (See Table 9.) Patients in Classes I and II (≤ 70 points) do not usually require hospitalization; patients in Class III (71-90 points) may require brief hospitalization, and those in Class IV (91-130 points) and Class V (> 130 points) usually require hospitalization.¹⁰⁵ In the derivation and validation of this rule, mortality was low for Classes I to III (0.1 to 2.8%), intermediate for Class IV (8.2% to 9.3%), and high for Class V (27% to 31.1%).⁹⁵

The British Thoracic Society developed the BTS Prediction Rule to help identify patients with community-acquired pneumonia who were at high risk. This rule defines a patient as being at high risk for death if at least 2 of 3 features are present — ie, respiratory rate ≥ 30 breaths per minute, diastolic blood pressure ≤ 60 mm Hg, and blood urea nitrogen (BUN) > 7.0 mM (> 19.1 mg/dL).¹⁰⁶ In another study, mental confusion was added as a fourth feature, and patients with any 2 of the 4 features were found to have a 36-fold increase in mortality compared with patients lacking these features.¹⁰⁷

The guidelines described above may certainly aid ED clinicians in deciding whether or not a patient can be safely discharged home on outpatient treatment. However, objective criteria or scores should be used as an adjunct to the ED clinician's overall subjective findings.^{xvii}

For example, a view of the patient's "social picture" will help the ED clinician make the correct decision when it comes to disposition. ED clinicians are certainly more inclined to admit a patient who, though less ill, is more likely to have difficulty obtaining medications and who is likely to be non-adherent, such as a homeless person, a substance abuser, or an elderly patient who lives alone. In such cases, admitting the patient to the hospital would prevent treatment failure and preclude the greater costs incurred owing to repeat visits or the need for critical care if the patient returns in a worse condition. The ED clinician can further assure the patient's reliability and compliance by providing clear instructions and explanations about the treatment plan.

Compliance With Drug Therapy

The issue of compliance is certainly one of the most important host factors. Making available a prescription plan will help alleviate the problem of "prescription resistance" and increase the likelihood of compliance. For patients without insurance coverage for prescription drugs, the cost of treatment must be

Table 9. Point Scoring System For Step 2 Of The PORT Pneumonia Prediction Rule For Assignment To Risk Classes II, III, IV, And V

Characteristic	Points Assigned*
Demographic Factor	
Age	
Men	+Age (in years)
Women	+Age (in years) –10
Nursing home resident	+10
Coexisting Illnesses	
Neoplastic disease [†]	+30
Liver disease [‡]	+20
Congestive heart failure [§]	+10
Cerebrovascular disease [•]	+10
Renal disease [¶]	+10
Physical Examination Findings	
Altered mental status [‡]	+20
Respiratory rate > 30 /min	+20
Systolic blood pressure < 90 mm Hg	+20
Temperature $< 35^\circ$ C or $> 40^\circ$ C	+15
Pulse > 125 /min	+10
Laboratory and Radiographic Findings	
Arterial pH < 7.35	+30
BUN > 30 mg/dL (11mmol/L)	+20
Sodium < 130 mmol/L	+20
Glucose > 250 mg/dL (14 mmol/L)	+10
Hematocrit $< 30\%$	+10
PaO ₂ < 60 mm Hg**	+10
Pleural effusion	+10

*A total point score for a given patient is obtained by adding the patient's age in years (age minus 10 (–10), for females) and the points for each applicable patient characteristic. Points assigned to each predictor variable were based on coefficients obtained from the logistic regression model used in step 2 of the prediction rule.

†Any cancer, except basal or squamous cell cancer of the skin, that was either active at the time of presentation or diagnosed within 1 year of presentation.

‡A clinical or histologic diagnosis of cirrhosis or other form of chronic liver disease, such as chronic active hepatitis.

§Systolic or diastolic ventricular dysfunction documented by history and physical examination, as well as chest radiography, echocardiography, multiple gated acquisition (MUGA) scanning, or left ventriculography.

•A clinical diagnosis of stroke, transient ischemic attack, or stroke documented by MRI or CT scan.

¶A history of chronic renal disease or abnormal blood urea nitrogen and creatinine values documented in the medical record.

#Disorientation (to person, place, or time, not known to be chronic), stupor, or coma.

**In the pneumonia PORT cohort study, an oxygen saturation value $< 90\%$ on pulse oximetry or intubation before admission was also considered abnormal.

Abbreviations: BUN, blood urea nitrogen; PaO₂, partial pressure of arterial oxygen; PORT, Patient Outcome Research Team.

a consideration, since the price of some antibiotics can be prohibitive. Choosing a less-expensive drug may be less than ideal but will improve the chances of achieving a clinical cure. In some communities, as many as 25% of patients may be unable to fill their prescriptions because of their excessive cost.¹⁰⁸ Remember, if you never get the antibiotic, it can't cure you. Opting for the generic version of a drug versus the brand-name product may also help lower the price for patients without prescription coverage.

Besides cost, the ED clinician must consider convenience (or lack thereof) as 1 aspect of prescribing medications. Here, the dosing frequency, length of therapy, and need for refrigeration all influence whether the patient will actually complete the course of therapy as directed.^{78,79,109,110} Patients are more likely to comply with a regimen when drugs are to be taken once or twice a day. The ideal scenario would be to prescribe well-tolerated, single-dose therapy (such as giving 1 g of oral azithromycin for chlamydia, or a 150-mg tablet of fluconazole for candida). Many of the newer regimens and medications are designed to take convenience into account. Prescribing antibiotics that taste good is of special

importance from the point of view of pediatric patients and their parents. Palatable medications are better accepted by toddlers and will decrease "parental resistance" to administering an antibiotic to the child. In general, cephalosporins and azithromycin tend to be preferred over penicillin, sulfa drugs, and erythromycin.

Special Considerations

Pregnancy

Pregnant and nursing patients deserve special considerations, as well. Not only are some drugs toxic to the fetus or breastfed infant, but the mother's metabolism is altered (eg, pregnancy results in lower serum levels of ampicillin). **(For a list of the most commonly used antibiotics and their safety for use in pregnancy, see Table 10.^{8,10})**

Outpatient Parenteral Antimicrobial Therapy

Outpatient parenteral antimicrobial therapy has been shown to be safe, efficacious, and cost-effective for carefully selected patients having a wide range of infectious diseases.¹¹²⁻¹¹⁵ Antibiotic use in these

Risk Management Pitfalls For Antibiotics In The ED (continued on page 113)

1. **"I had to wait for the CT results before doing the LP. That's why the antibiotics were delayed."**
It is now common knowledge that antibiotics should be administered immediately when the diagnosis of meningitis is a strong possibility. The LP can be performed without obtaining a prior CT scan, as long as there are no features in the clinical presentation that suggest a mass lesion with increased intracranial pressure.¹¹⁷ An LP should also not be performed without a prior CT scan in the case of a comatose patient, since an adequate neurological examination is not possible. Do not withhold the administration of antibiotics for the LP. There is no evidence that antibiotic treatment will interfere with making the diagnosis of meningitis.
2. **"She didn't tell me that she was allergic to penicillin."**
It is the ED clinician's responsibility to obtain an adequate history. Questions about medication allergies are very important, especially when treating someone with antibiotics. Remember, the most frequent adverse effect of antibiotics is allergic reaction, and the patient may not volunteer this information. Don't even rely on a negative "check off" by the nurses. Always ask the patient yourself!

3. **"Cefotetan is a cephalosporin, and they are always safe to prescribe in patients with renal failure."**
When administering antibiotics to patients with underlying disease, you have to ensure the dose does not require adjustments. In renal failure, some antibiotics only require adjustment of the interval between doses, but most of them need both dose and interval adjustment.
4. **"I treated her for a simple UTI. She didn't tell me she was on anticoagulants."**
Another "must" is obtaining a medication history. Many antibiotics will alter the metabolism of other medications taken by the patient and complicate their side effects (eg, bleeding in the anticoagulated patient when the action of warfarin is potentiated by the administration of ciprofloxacin).
5. **"He needed an antibiotic for his pneumonia. I did not know someone had started him on theophylline for his asthma."**
Again, medication history is vital. Prescribing antibiotics should not cause serious iatrogenic disease. Even a seemingly benign medication like erythromycin has been reported to induce theophylline toxicity by increasing theophylline levels.

instances also reduces the risk of contracting a hospital-acquired infection — an important added benefit. Skin and soft tissue infections, osteomyelitis, joint infections, bacteremia, endocarditis, pulmonary infections, and ENT infections have been effectively treated with outpatient parenteral antimicrobial therapy. To be considered candidates for such therapy, patients must meet the following 3 criteria:

1. Patients must have an active infectious disease that requires treatment beyond the expected hospital stay.
2. There should be no need for hospitalization other than the infectious disease.
3. There must be no equally safe and effective oral antibiotic therapy available.¹¹⁶

Summary

Infections are a source of significant morbidity and mortality. Antibiotics can be lifesaving and, if used appropriately, can prevent complications in the battle against these invaders. When selecting an antibiotic in the ED, clinicians must rely on the char-

acteristics of 3 primary factors to guide their choices: the most likely pathogen (the bug), the antibiotic (the drug), and the patient (the host).

The site of infection is of paramount importance in determining which bugs need to be covered. It can usually be discerned during the clinical evaluation (history and physical examination) and confirmed with appropriate laboratory tests. The resistance pattern of the suspected pathogen should also be considered. It is important to be familiar

Table 10. Safety Of Selected Antibiotics In Pregnancy

Generally Safe	Unsafe
Penicillins	Aminoglycosides
Cephalosporins	Imipenem
Macrolides (except clarithromycin)	Quinolones
	Tetracyclines
	Sulfonamides (third trimester)

Risk Management Pitfalls For Antibiotics In The ED (continued from page 112)

6. **“I thought that patient just had a bad cold.”**
While it is certainly prudent to withhold antibiotics when the infection is likely viral in origin, before doing so you must weigh all the “special” circumstances. Is this an older, febrile patient? Is the patient immunocompromised or diabetic? Take care that you are not missing a bacterial infection that may lead to overwhelming sepsis.
7. **“I put him on penicillin, and penicillin always covers *Streptococcus*.”**
In the current era of increasing antibiotic resistance in several major “bugs,” always consider the possibility of a resistant strain. This is particularly important in patients who appear to be very ill or who have an infection at an “unforgiving” site, like the meninges. Bacterial susceptibility tables provided by your hospital laboratory should aid in selecting the right treatment.
8. **“I didn’t know she was pregnant.”**
Well, if the woman was of childbearing age, you should have considered the possibility! Many “ED favorites” among antibiotics are contraindicated during pregnancy (eg, fluoroquinolones, tetracyclines, and clarithromycin). Similarly when treating the pediatric population, your available choices may be limited, as well.
9. **“That nursing home patient was diagnosed with pneumonia, so azithromycin was an appropriate treatment.”**
Or was it? Institutionalized patients may have unusual etiologies for common infections. Azithromycin would be a fine choice for community-acquired pneumonia, but you have to consider more than just the site of infection. A history of recent hospitalization will also alter the spectrum of possible pathogens, as will other historical factors, such as seizures or alcoholism.
10. **“I put her on antibiotics. That should have cured the skin infection.”**
Not always! Sometimes, more than antibiotics are required. If there is a pus collection, it must be drained. A foreign body, if present, should be removed. In some rapidly progressing infections, such as necrotizing fasciitis, get the surgeon involved early, in case fasciotomy is needed. Always remember that atypical pathogens may be involved, particularly if there is a history of animal or human bite. (For more information on bites of an unusual nature, see *Emergency Medicine Practice*, Volume 5, Number 8, “Dog, Cat, And Human Bites: Providing Safe And Cost-Effective Treatment In The ED,” August 2003, and *Pediatric Emergency Medicine Practice*, “Evidence-Based Management Of Mammalian Bite Wounds,” September 2009.)

with the characteristics of the most commonly used antibiotics, including their spectrum of coverage and toxicity. "Host factors" must be considered as well, particularly the severity of the patient's disease, underlying illnesses, and social factors, since they all affect the choice of antibiotics as well as decisions regarding disposition of the patient.

Here we have provided guidelines to help ED clinicians choose antibiotics for treating the most common infections encountered in the ED. When applying these guidelines in any specific patient, however, the basic bug/drug/host approach is always the one to use.

Case Conclusion

10/15

Dear Diary,

Went in to check up on my urosepsis patient and was happy to see that she had improved dramatically. She had been extubated and was in a regular bed pending discharge. In the interim, I had read Emergency Medicine Practice "Antibiotics in the ED" and realized that in the elderly, I should have considered other causes for her fever. My antibiotics did not ultimately cover her for urosepsis (probably caused by gram (-) bacteria). Thankfully, in this case, the patient ultimately recovered and was happy to go home.

References

Evidence-based medicine requires a critical appraisal of the literature based on study methodology and number of participants. Not all references are equally robust. The findings of a large, prospective, randomized, and blinded trial should carry more weight than a case report

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The following new references have been added by the editor for this revised version.

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CME Questions

47. For which one of these viral infections do we have an effective therapy for active disease?
- Poliomyelitis
 - Rabies
 - Herpes simplex infection
 - West Nile encephalitis
 - The common cold
48. A previously healthy young man returns from vacation in the Amazon basin complaining of high fevers and shaking chills. Which one of the following infections must we consider especially?
- Rocky Mountain spotted fever
 - Gonorrhea
 - Legionellosis
 - Malaria
 - Urosepsis
49. A previously healthy young woman presents with fever, dysuria, and flank pain. The most likely pathogen causing her symptoms is:
- S pneumoniae*
 - H influenzae*
 - S aureus*
 - B fragilis*
 - E coli*
50. A young woman presents with a high fever and appears to be toxic. Her history is noteworthy only for a splenectomy due to a car accident 10 years previously. The pathogens that you would have to especially consider and treat for are:
- Gram-negative organisms: *E coli*, *K pneumoniae*
 - Encapsulated organisms: *S pneumoniae*, *H influenzae*
 - Anaerobes: *Bacteroides fragilis*, *Clostridium welchii*
 - Pneumocystis*, *Cryptococcus*, and *Toxoplasma*
 - S aureus* and *S pyogenes*
51. A potential long-term side effect of using broad-spectrum antibiotics is:
- Genetic mutations in the human race
 - Bankruptcy of the pharmaceutical companies
 - Emergence of resistant organisms
 - Lack of adequate coverage leading to chronic infection
 - Poor patient compliance
52. First-generation cephalosporins cannot be used to treat meningitis because:
- They do not adequately penetrate the blood-brain barrier
 - The most likely pathogens are resistant to them
 - They are bacteriostatic drugs
 - Their side effects are usually not tolerated
 - They are extremely expensive
53. Which class of antibiotics should generally be avoided in young children?
- Penicillins
 - Aminoglycosides
 - Macrolides
 - Sulfonamides
 - Tetracyclines
54. The key reason patient compliance with the "newer" antibiotics is better than with the "old" ones is:
- The new antibiotics are less expensive.
 - The new antibiotics have less serious toxicity.
 - The new antibiotics are usually taken just once or twice daily.
 - The new antibiotics cause less bacterial resistance.
 - The new antibiotics get more advertising.
55. Bronchitis should probably be treated with antibiotics in:
- Diabetics
 - Young patients
 - Patients with other symptoms of upper respiratory infection
 - COPD
 - Pregnant patients
56. The safest antibiotic to use for urinary tract infection in a pregnant patient is:
- An aminoglycoside
 - A cephalosporin
 - A fluoroquinolone
 - Doxycycline
 - Trimethoprim/sulfamethoxazole
57. In an otherwise healthy child who is not toxic and who presents with an uncomplicated first-time otitis media, first-line therapy would usually be:
- Amoxicillin
 - A new macrolide
 - Amoxicillin/clavulanic acid
 - Fluoroquinolone
 - Clindamycin

58. **Different antibiotics should never be used in combination, due to potential toxicity.**
- True
 - False
59. **Which antibiotic is not recommended for outpatient treatment of community-acquired pneumonia in adults?**
- Fluoroquinolone
 - Doxycycline
 - A new macrolide
 - Amoxicillin
60. **Which is a recommended regimen for outpatient treatment of PID?**
- Ceftriaxone IM followed by oral doxycycline
 - Amoxicillin/clavulanic acid
 - Azithromycin 1 gram single oral dose
 - Cefotetan and doxycycline
 - Metronidazole
61. **For a patient in whom you strongly suspect bacterial meningitis, which is most prudent?**
- Do not give antibiotics until the LP results are back.
 - Do not give antibiotics until the CT is done.
 - You always need the CT before the LP.
 - Give appropriate antibiotics immediately, even if the LP is delayed.
62. **Of the following patients with pneumonia, whom would you most likely admit?**
- The one with a good insurance plan
 - An elderly patient who lives alone
 - A 2-year-old with reliable parents
 - A penicillin-allergic patient

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The Young Febrile Child

1. ____ Explain important aspects of the history and physical examination in children with fever; list indications for diagnostic tests in febrile children, including CBC, lumbar puncture, chest x-ray, urinalysis, and urine culture; describe the risks and indicators of occult bacteremia; and discuss the evidence concerning empiric antibiotic treatment in febrile children.

Pharyngitis In The ED

2. ____ Discuss how the history and physical examination can identify causes of pharyngitis or determine the need for diagnostic testing, and how clinical decision rules may aid in this process; discuss the utility and limitations of different diagnostic studies used in evaluating patients with pharyngitis; discuss the identification and management of serious and/or potentially life-threatening causes of pharyngitis; describe how to identify and manage GABHS in adults and children; and describe appropriate treatment, such as antibiotic therapy and/or pain management, for patients with pharyngitis.

HIV-Related Illnesses

3. ____ Assess a patient's risk of being infected with HIV, describe the importance of the CD4 count in determining the stage of infection, and evaluate the risk of infection with opportunistic pathogens; describe the most common CNS, gastrointestinal, and respiratory complications of HIV-associated disease as well as their proper evaluation and treatment; evaluate and manage the febrile AIDS patient; and describe the most common side effects and toxicities of drugs used to treat HIV infection and AIDS.

Antibiotics In The ED

4. ____ Discuss important factors in choosing antibiotics for ED use; describe the important characteristics of the classes of antibiotics most commonly used in the ED; identify and discuss common clinical and medicolegal problems and pitfalls that occur when treating infections in the ED; and choose appropriate antibiotics for the infections most commonly encountered in the ED.

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2. ____ Discuss how the history and physical examination can identify causes of pharyngitis or determine the need for diagnostic testing, and how clinical decision rules may aid in this process; discuss the utility and limitations of different diagnostic studies used in evaluating patients with pharyngitis; discuss the identification and management of serious and/or potentially life-threatening causes of pharyngitis; describe how to identify and manage GABHS in adults and children; and describe appropriate treatment, such as antibiotic therapy and/or pain management, for patients with pharyngitis.

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3. ____ Assess a patient's risk of being infected with HIV, describe the importance of the CD4 count in determining the stage of infection, and evaluate the risk of infection with opportunistic pathogens; describe the most common CNS, gastrointestinal, and respiratory complications of HIV-associated disease as well as their proper evaluation and treatment; evaluate and manage the febrile AIDS patient; and describe the most common side effects and toxicities of drugs used to treat HIV infection and AIDS.

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| 18. [a] [b] [c] [d] [e] | 51. [a] [b] [c] [d] [e] |
| 19. [a] [b] [c] [d] [e] | 52. [a] [b] [c] [d] [e] |
| 20. [a] [b] [c] [d] [e] | 53. [a] [b] [c] [d] [e] |
| 21. [a] [b] [c] [d] [e] | 54. [a] [b] [c] [d] [e] |
| 22. [a] [b] [c] [d] [e] | 55. [a] [b] [c] [d] [e] |
| 23. [a] [b] [c] [d] [e] | 56. [a] [b] [c] [d] [e] |
| 24. [a] [b] [c] [d] [e] | 57. [a] [b] [c] [d] [e] |
| 25. [a] [b] [c] [d] [e] | 58. [a] [b] [c] [d] [e] |
| 26. [a] [b] [c] [d] [e] | 59. [a] [b] [c] [d] [e] |
| 27. [a] [b] [c] [d] [e] | 60. [a] [b] [c] [d] [e] |
| 28. [a] [b] [c] [d] [e] | 61. [a] [b] [c] [d] [e] |
| 29. [a] [b] [c] [d] [e] | 62. [a] [b] [c] [d] [e] |
| 30. [a] [b] [c] [d] [e] | |
| 31. [a] [b] [c] [d] [e] | |
| 32. [a] [b] [c] [d] [e] | |
| 33. [a] [b] [c] [d] [e] | |

Please continue test and complete Evaluation Form on reverse side.

An Evidence-Based Approach To Infectious Disease CME Evaluation Form

Please record actual time spent on this activity here, if less than designated time of 16 hours: _____

Please take a few moments to complete this form. Your opinions will ensure continuing program relevance and quality.

Enter the extent to which you agree with the following statements. Response codes: **5=strongly agree; 4=agree; 3=neutral; 2=disagree; 1=strongly disagree**

1. ____ The chapters were easy and enjoyable to read.
2. ____ The information was presented in an impartial and unbiased manner, and the authors were not biased in their discussion of any commercial product or service.
3. ____ Adequate faculty disclosure was given.
4. ____ This activity improved my competence.
5. ____ This activity improved my performance.
6. ____ This activity improved outcomes for my patients.

Enter the extent to which the following objectives were met for each chapter.

The Young Febrile Child

1. ____ Explain important aspects of the history and physical examination in children with fever; list indications for diagnostic tests in febrile children, including CBC, lumbar puncture, chest x-ray, urinalysis, and urine culture; describe the risks and indicators of occult bacteremia; and discuss the evidence concerning empiric antibiotic treatment in febrile children.

Pharyngitis In The ED

2. ____ Discuss how the history and physical examination can identify causes of pharyngitis or determine the need for diagnostic testing, and how clinical decision rules may aid in this process; discuss the utility and limitations of different diagnostic studies used in evaluating patients with pharyngitis; discuss the identification and management of serious and/or potentially life-threatening causes of pharyngitis; describe how to identify and manage GABHS in adults and children; and describe appropriate treatment, such as antibiotic therapy and/or pain management, for patients with pharyngitis.

HIV-Related Illnesses

3. ____ Assess a patient's risk of being infected with HIV, describe the importance of the CD4 count in determining the stage of infection, and evaluate the risk of infection with opportunistic pathogens; describe the most common CNS, gastrointestinal, and respiratory complications of HIV-associated disease as well as their proper evaluation and treatment; evaluate and manage the febrile AIDS patient; and describe the most common side effects and toxicities of drugs used to treat HIV infection and AIDS.

Antibiotics In The ED

4. ____ Discuss important factors in choosing antibiotics for ED use; describe the important characteristics of the classes of antibiotics most commonly used in the ED; identify and discuss common clinical and medicolegal problems and pitfalls that occur when treating infections in the ED; and choose appropriate antibiotics for the infections most commonly encountered in the ED.

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1. What clinical information did you learn that was of value to you, and how did this information impact positively or change the way you care for your patients? _____

2. Please provide any additional comments. _____

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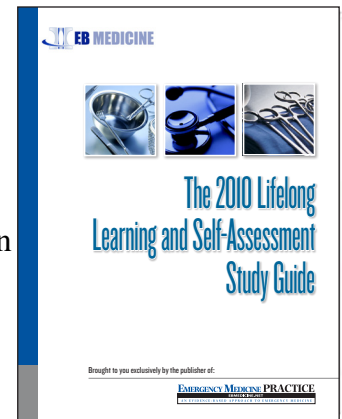
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