

Fever and the Rational Use of Antimicrobials in the Emergency Department

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KEYWORDS

- Fever • Antibiotics • Antivirals • Antifungals • Antimicrobial resistance
- Hospital-acquired infections

KEY POINTS

- Emergency physicians must balance public health concerns about increasing antimicrobial resistance with the need for early antimicrobial therapy in febrile, ill patients.
- Institutional antibiograms should help guide antibiotic choices.
- Antimicrobial choices are affected by factors such as cost, dosing frequency, side effects, administration route, and infusion properties.
- Empiric antimicrobial therapy is challenging and ever-changing; it is the responsibility of the emergency physician to remain up to date.

INTRODUCTION

According to the 2009 National Hospital Ambulatory Medical Survey, 5.6% of patients who sought treatment in emergency departments (EDs) were febrile at the time of presentation. Second only to abdominal pain and cramps, fever was the second most common chief complaint for patients who came to EDs that year, and the most common chief complaint of patients younger than 15 years. The presence of fever prompts the question of whether antimicrobials should be administered empirically. The survey data also indicate that antimicrobials were the most prescribed drug category, second only to analgesics.¹ In EDs around the United States, 7% to 8% of visits involve the administration of at least 1 antimicrobial.²

Antimicrobials are ordered in the ED every day. Sometimes the indication is straightforward and the choices are simple; at other times the decisions are more

The authors have no conflicts of interest to disclose.

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Emerg Med Clin N Am 31 (2013) 945–968
<http://dx.doi.org/10.1016/j.emc.2013.07.007>

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difficult. Any patient presenting with fever triggers consideration of the administration of an antimicrobial. Frequently, the decision to initiate empiric treatment needs to be made before the definitive diagnosis is known. In such cases, an organized approach is helpful.³⁻⁵

Determining the cause of a fever and subsequently treating it appropriately depend on multiple factors. Ideally each patient enters the ED with a clear history, and classic physical examination findings and the results of diagnostic tests mark an obvious path. However, a thorough history and physical examination can be hindered by uncontrollable elements, such as altered mental status. Results of diagnostic tests can be equivocal or even false. Therefore, empiric antimicrobial therapy has become a cornerstone of treatment. How does the emergency physician balance responsible stewardship of health resources with the need to provide effective treatment promptly?

The goal of this review is to provide a systems-based approach to prescribing antimicrobials to patients presenting to the ED with fever, while understanding the risk associated with overutilization. It seeks to provide an understanding of the key considerations needed to ensure that decisions are made well and appropriate treatment begins promptly.

GENERAL CONSIDERATIONS

When Should Antimicrobials be Used Empirically?

Not uncommonly, a physician decides that antimicrobials are needed even though a definitive infectious diagnosis has not yet been established. In these cases, “empiric therapy” is initiated, targeting potential sources of infection deemed likely and serious.⁶ The spectrum of coverage is guided by a preliminary impression of probable infectious site based on the history and physical examination, relevant demographic information, medical history, laboratory data, and results of diagnostic imaging. Therefore, a good understanding of the surrounding epidemiology is particularly important. Many hospitals routinely gather culture results and sensitivity data for analysis and construction of a hospital antibiogram that provides antibiotic recommendations linked to specific clinical scenarios. This information is particularly useful for emergency service providers and others who see patients early in the course of illness, before cases have been definitively differentiated.

The need to administer antibiotics early and empirically is particularly pressing in the setting of severe infectious illnesses, including sepsis, pneumonia, and meningitis. Although some controversies remain, it is well established that antibiotics need to be administered empirically and early in selected cases, based on clinical judgment.² A particularly well-known illustration is found in the work of Emanuel Rivers and others, in which the strategy known as early goal-directed therapy⁵ showed a significant positive impact on outcomes among patients with septic shock.⁶ The 2012 Surviving Sepsis Guidelines emphasize administration of effective antimicrobials within the first hour after recognition of severe sepsis or septic shock.⁷

Assessing Vulnerability of the Patient

Comorbid conditions

The decision to prescribe antimicrobials can be informed by a thorough assessment of variables related to the host.⁸ Some patients are unable to tolerate certain treatments because of hypersensitivity reactions. Patients might report a history of “allergy” in the past, even though no true allergy exists. It is important to investigate whether a history of intolerance is based on a true allergy or a less serious problem; for example, a

patient might have experienced gastrointestinal distress after taking a macrolide in the past, and therefore refuses to take it despite not having a true hypersensitivity reaction to the antibiotic.⁹

Patients with acute or chronic organ dysfunction might require antibiotic strategies that deviate from routine standard approaches. A particularly common example is renal dysfunction. Renal failure (whether acute or chronic) can affect elimination of antibiotics, which should be considered when establishing the appropriate dose and timing interval of antibiotics that are cleared by the kidneys. In addition, some antibiotics can directly cause renal or hepatic toxicity, and should be avoided in patients with underlying disease.

Immunocompromised patients raise particularly important issues. Such patients are exposed to all of the same common pathogens that infect otherwise healthy individuals and, at the same time, are particularly susceptible to atypical infections, including fungal infections and infections with resistant or particularly virulent organisms (eg, *Pseudomonas*) to which immunocompetent patients are less vulnerable. Understanding the host's response to the infection can have a significant impact on treatment choices and timing. Immunocompromised hosts can present atypically; they may not mount a fever and may not show classic signs of severity until late in the disease course. This situation could lead to delayed administration of antibiotics and failure to manage the patient aggressively on initial presentation.²

Drug interactions and side effects

Drug interactions can heighten patients' vulnerability to certain complications. For example, patients on warfarin for anticoagulation therapy may need to avoid fluoroquinolones to prevent coagulopathy. When quinolones must be used (or have been used inadvertently), it is essential to check the international normalized ratio to monitor coagulation status. Similarly, patients who are receiving metronidazole should be advised to avoid alcohol, because of the associated disulfiram-like reaction of nausea, vomiting, flushing of the skin, and tachycardia.

Socioeconomic status

Although not a comorbid medical condition per se, socioeconomic variables can render patients more vulnerable to infection and less able to access appropriate treatment. When financial barriers are significant, the cost of medicines needs to be considered in relation to patients' capacity to comply with recommendations. When patients are discharged with recommended outpatient follow-up, the cost of an antimicrobial and its dosing schedule become significant drivers of adherence. Generic brands that can be found in the formularies of large pharmacies are typically more affordable. Medicines that require frequent dosing are more difficult to take correctly and, as a result, compliance with therapy might be suboptimal.

Useful Clues to Support Targeting of Empiric Antibiotics

Identifying probable site(s) of infection

The history and physical examination, coupled with laboratory tests and imaging, should help identify the site of possible infection in a patient presenting with fever to the ED. Some sites of infection are difficult to penetrate with antibiotics, given the anatomy of the blood flow, and therefore limit the concentration of the antibiotic that can reach that organ. Areas that suffer significantly from lower concentrations of antibiotic include the cerebrospinal fluid (CSF), the prostate, the pancreas, the skin, soft tissue in patients with poorly controlled diabetes or peripheral vascular disease, and the vitreous humor of the eye.⁹

Which pathogens are most likely?

If multiple antibiotics are to be administered, consider first giving the antibiotic that is most likely to attack the offending organism, with guidance from the systems-based review that follows. For example, in a diabetic nursing-home patient at risk for *Pseudomonas aeruginosa*, the most likely cause of pneumonia remains a gram-positive coccus; therefore, *Streptococcus pneumoniae* should be targeted first, after which the need to also cover *P aeruginosa* should be addressed.

Using Antimicrobials Wisely and Strategically

Timing and sequence of administration

When choosing empiric antimicrobials, it is important to consider the pharmacokinetic and practical features of the options under consideration. For example, the combination of piperacillin-tazobactam and vancomycin is commonly used to provide broad-spectrum coverage when the prescribing physician judges that both methicillin-resistant *Staphylococcus aureus* (MRSA) and *P aeruginosa* need to be covered empirically. Typically, piperacillin-tazobactam can be administered more rapidly than vancomycin, so it may be prudent to give piperacillin-tazobactam first.

Considerations specific to route of administration

Intravenous antimicrobials might be preferred to oral options when the need to achieve an effective therapeutic index rapidly is judged to be particularly pressing. Though somewhat controversial, a common strategy is to administer a single dose of intravenous antibiotics followed by an oral agent that provides similar coverage but requires more time to reach effective therapeutic levels. For example, a patient can be given a dose of intravenous ampicillin-sulbactam followed by oral amoxicillin-clavulanate. Although research to support this approach is limited, it arguably combines the desired effects of early arrival at an effective therapeutic level with the practical preference for outpatient management in appropriately selected patients.¹⁰

Mode of action: bactericidal versus bacteriostatic

Bactericidal drugs kill bacteria, whereas bacteriostatic drugs inhibit cell growth. Drugs that are bactericidal do not need to reach near the concentration that bacteriostatic drugs are required to reach to kill the organism. Bactericidal drugs often kill at 4 times the mean inhibitory concentration (MIC), whereas bacteriostatic drugs may not kill until they reach a concentration of 16 times the MIC. Therefore, when considering infections in locations with poor blood flow, such as the prostate, or when treating a patient with significant microvascular disease (eg, a person with poorly controlled diabetes), bactericidal drugs might be more beneficial in reaching effective concentrations in the host's infected tissues without reaching toxic levels in other organ systems.

Despite the 4-fold difference in efficacy, bacteriostatic drugs play an important role in treating infections. Bacteriostatic agents contain the growth of an organism and allow the host's immune system to fight the infection. Specific features of the patient must be considered when predicting whether the host will be able to mount a sufficient response to fight the infection that remains. Bactericidal agents are preferred for patients who are immunocompromised or neutropenic, and those who have endovascular infections (endocarditis, meningitis, or cerebral abscess) or osteomyelitis.⁹ Bacteriostatic antibiotics can be particularly beneficial in disease processes caused by organisms that divide rapidly or produce toxins that are targeted by the antibiotic: for example, toxic shock syndrome is a systemic manifestation of group A streptococci (GAS) infection secondary to the toxin produced by the GAS. Clindamycin, though bacteriostatic, is the drug of choice in this situation, because its mechanism of action decreases toxin production and thereby lessens systemic symptoms (**Table 1**).

Table 1
Pharmacokinetic properties of major antibiotic classes

| Antibiotic | Mechanism of Action | Targeted Microbes | Special Considerations |
|---|---|---|--|
| Penicillins (β -lactam) | BACTERICIDAL: Inhibit cell-wall synthesis, exposing unstable membranes, leading to cell lysis | Gram-positive, some gram-negative coverage | |
| β -Lactamase inhibitor (clavulanate, sulbactam, tazobactam) | Augment utility of β -lactam-ring-based antibiotics by inhibiting enzymatic breakdown | Extends spectrum of many penicillins to target resistant organisms and more gram-negative coverage | |
| Cephalosporins (β -lactam) | BACTERICIDAL: Inhibit cell-wall synthesis, exposing unstable membranes, leading to cell lysis, but less susceptible to β -lactamase | | Some of the less commonly used inhibit vitamin K production and cause disulfiram-like reaction (eg, cefotetan) |
| | First generation (cephalexin, cefazolin) | Gram-positive cocci, gram-negative bacilli (<i>Proteus</i> , <i>Escherichia coli</i> , <i>Klebsiella</i>) | |
| | Second generation (cefaclor, cefuroxime, cefotetan, cefoxitin) | Gram-positive cocci, gram-negative cocci (<i>Neisseria gonorrhoeae</i>), gram-negative bacilli (<i>Enterobacter</i> , <i>E coli</i> , <i>Haemophilus influenzae</i> , <i>Klebsiella</i> , <i>Proteus</i>) | |
| | Third generation (cefдинир, cefixime, cefotaxime, cefpodoxime, ceftriaxone, ceftazidime) | Broader gram-negative coverage (<i>Pseudomonas</i> covered by ceftazidime) | Ceftriaxone is excreted in bile |
| | Fourth generation (cefepime) | Staphylococci, streptococci, and gram-negative bacilli (including <i>Pseudomonas</i>) | |
| | Fifth generation (ceftaroline) | Gram-positive cocci, gram-negative bacilli, MRSA (only SSTI) | |

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Table 1
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| Antibiotic | Mechanism of Action | Targeted Microbes | Special Considerations |
|--|---|---|--|
| Carbapenems (meropenem, imipenem, ertapenem, doripenem) | BACTERICIDAL: Inhibit cell-wall synthesis, exposing unstable membranes, leading to cell lysis, but less susceptible to β -lactamase | Penicillinase gram-positive and gram-negative organisms, anaerobes, and <i>Pseudomonas</i> | |
| Monobactams (aztreonam) | BACTERICIDAL: Inhibit cell-wall synthesis, exposing unstable membranes, leading to cell lysis but less susceptible to β -lactamase | Gram-negative only, including pseudomonas | Should be reserved for identified resistance; limit empiric use. |
| Vancomycin | BACTERICIDAL: Inhibit cell-wall synthesis, exposing unstable membranes, leading to cell lysis but less susceptible to β -lactamase | Gram-positive, including MRSA and enterococci | Oral use reserved for <i>Clostridium difficile</i> infection only Very broad coverage when combined with aminoglycoside Administer 1 g/h to prevent red man syndrome |
| Tetracyclines (doxycycline, minocycline) | BACTERIOSTATIC: Inhibit protein synthesis by reversibly binding ribosomes blocking tRNA | Gram-positive and some gram-negative; atypical or intracellular organisms (such as <i>Chlamydia</i> , <i>Mycoplasma</i> , and tick-borne disease) | Substantial bacterial resistance TERATOGENIC: causes discoloration and hypoplasia of bones and teeth, fetal hepatotoxicity |
| Aminoglycosides (amikacin, gentamicin, tobramycin, streptomycin) | BACTERICIDAL (based on concentration and dosing intervals): Inhibit protein synthesis by binding to ribosome subunit, preventing full ribosome assembly | Gram-negative (includes <i>Pseudomonas</i>) | Activity augmented when preceded by a penicillin |

| | | | |
|--|---|---|---|
| Macrolides (erythromycin, clarithromycin, azithromycin, telithromycin) | BACTERIOSTATIC: Inhibit protein synthesis by irreversibly binding ribosomes, preventing translocation | Atypical or intracellular organisms (such as <i>Chlamydia</i> , <i>Legionella</i> , <i>Mycoplasma</i>) | |
| Clindamycin | BACTERIOSTATIC: Inhibit protein synthesis by binding ribosomes, preventing translocation | Gram-positive (including MRSA), anaerobic bacteria | Most frequent culprit of <i>C difficile</i> infection Used for toxin-producing infections such as toxic shock syndrome |
| Linezolid | BACTERIOSTATIC: Inhibit protein synthesis by preventing full ribosome complex formation (bactericidal against certain organisms) | Gram-positive (MRSA, VRE, <i>Listeria</i>) | |
| Fluoroquinolones (levofloxacin, moxifloxacin, ciprofloxacin) | BACTERICIDAL (dose dependent): Inhibit DNA gyrase and topoisomerase, preventing DNA replication causing cell death, and blocks cell division by not allowing new DNA to segregate | Gram-negative (some <i>Pseudomonas</i>), gram-positive (no MRSA) and atypical organisms | TERATOGENIC: affects connective tissue development |
| Sulfonamides (trimethoprim-sulfamethoxazole) | BACTERIOSTATIC: Inhibit synthesis of bacterial folic acid preventing formation of essential cofactors | Gram-positive (MRSA), limited gram-negative | Severe hypersensitivities including SJS Can elicit hemolytic anemia in patients with G6PD |
| Metronidazole | BACTERICIDAL: forms unstable molecules within DNA | Anaerobic bacteria and protozoa | Biliary excretion allows it to be effective against <i>C difficile</i> |

Abbreviations: G6PD, glucose-6-phosphate dehydrogenase; MRSA, methicillin-resistant *Staphylococcus aureus*; SJS, Stevens-Johnson syndrome; VRE, vancomycin-resistant enterococci.

GROWING ANTIBIOTIC RESISTANCE IN THE UNITED STATES

Data from the Centers for Disease Control and Prevention (CDC) demonstrate that resistance persists as a growing public health concern. Unless significant action is taken in altering the way antibiotics are stewarded by physicians, organisms that are resistant to the newest and strongest antibiotics will continue to emerge. In November 2012, the National Institutes of Health (NIH) and the Pew Health Group published a study highlighting the absolute necessity of improving prescribing habits and educating patients.^{11,12} Many Americans understand the importance of antibiotic resistance and know that the full course of prescribed antibiotics should be taken, even if they do not always comply with such recommendations. Patients believe that organisms are becoming resistant to antibiotics in the community, but they have low suspicion that the organisms will affect them or a family member.¹¹ As physicians, our role in patient education and taking responsibility to not overprescribe antibiotics is of the utmost importance. Prescribing rates for antibiotics have fallen 17% nationwide since 1999, although some states have had more progress than others.¹³ Emergency physicians frequently feel pressured by patients to prescribe antibiotics.

The number of antibiotics and other antimicrobials being developed has fallen drastically over the past several decades. From 1983 to 1987, pharmaceutical companies introduced 16 new antimicrobial agents to the market. Since then there has been a steady decline in production; between 2003 and 2007, only 5 new antibiotics were introduced, and since 2007 only 1 new agent has been developed.¹⁴ The Pew Health Group identified several challenges to antibiotic innovation. Scientifically, new classes of antibiotic with novel mechanisms of action are difficult to discover. Economically, antibiotics produce lower revenues than other pharmaceuticals. In addition, achieving approval for a new antibiotic from the US Food and Drug Administration (FDA) has become more challenging, because investigators find it difficult to amass a sufficient number of study subjects and regulatory measures are tighter, requiring that the new agent must show improved efficacy and decreased adverse reactions or toxicity.¹³

The financial burden associated with resistant organisms is increasing. The CDC estimates that each year, resistant infections account for about \$20 billion management costs and contribute to an estimated 8 million additional hospital days.^{14,15} An increasing number of organisms have been identified as having resistant strains in North America and abroad. The most prevalent drug-resistant pathogens cited by the CDC are *Acinetobacter*, group B streptococci, *Klebsiella pneumoniae*, MRSA, *Neisseria meningitidis*, *Shigella*, *S pneumoniae*, vancomycin-resistant enterococci, *Candida*, and the human immunodeficiency virus (HIV) and the organisms that cause anthrax, gonorrhea, tuberculosis, typhoid fever, influenza, and malaria.¹⁶ Therefore, in times of increasing resistance, the most efficacious antibiotic should be deployed, which will create the least amount of inducible resistance within the host and deliver the most precise targeting to the susceptible organism and the affected organ system.

TARGETED ANTIMICROBIAL THERAPY BY SYSTEM

Central Nervous System

Meningitis and encephalitis

Meningitis and encephalitis secondary to bacterial infection confer significant risk of morbidity and mortality. Early diagnosis and treatment remain essential to averting death and disabling neurologic sequelae. Typical presentations warrant empiric treatment, including appropriately timed diagnostic studies and early antibiotics. Atypical presentations pose diagnostic challenges, emphasizing the importance of maintaining

a high index of suspicion for these conditions, and carefully considering the timing and sequencing of therapeutic efforts.

Although incidental cases of bacterial meningitis and encephalitis are relatively rare, they are considered true neurologic emergencies. When meningitis or encephalitis is suspected, empiric administration of the appropriate antibiotic should be seriously considered as early as possible. Proulx and colleagues¹⁷ demonstrated that patients who receive antibiotics in the ED are significantly less likely to die than patients who do not receive antibiotics before arrival at the inpatient service (mortality rates of 7.9% and 29%, respectively). Other studies have shown a less robust effect of early antibiotic administration.² Typical manifestations of meningitis/encephalitis are fever, headache, nuchal rigidity, and altered mental status.¹⁸ The clinical syndrome of fever and headache should prompt consideration of meningoencephalitis, although these symptoms are nonspecific.

Evaluation and diagnosis

Appropriate evaluation includes certain diagnostic tests that may cause significant delays in definitive therapy. In particular, the appropriateness and timing of computed tomography (CT) of the head, lumbar puncture, and blood cultures need to be considered in relation to the expected clinical benefits compared with earlier administration of antibiotics and, possibly, steroids. The Infectious Diseases Society of America (IDSA) guidelines for bacterial meningitis emphasize that blood cultures should be obtained and lumbar puncture performed promptly (before administration of parenteral antibiotics and steroids when it has been determined that a head CT scan is not needed).¹⁹

Analysis of cerebrospinal fluid

Analysis of CSF allows the differentiation of bacterial from viral meningitis. A positive Gram stain points convincingly toward a bacterial source, whereas a negative Gram stain cannot exclude an occult bacterial infection. CSF cell counts and chemistries are expected to demonstrate typical patterns corresponding to either a viral or bacterial source. Nevertheless, results sometimes will be equivocal. CSF cultures can also be useful, but require 24 to 48 hours to provide useful information.^{20,21}

Other candidate markers in the CSF, including lactate and procalcitonin levels, are under active investigation as correlates of bacterial meningitis, but evidence to recommend their routine use is lacking.¹⁹ Imperfect prediction of bacterial meningitis based on CSF analysis emphasizes the point that empiric therapy for bacterial infection could be prudent regardless of test results in selected cases.

Treatment

Cases requiring prompt treatment of bacterial meningitis have (1) typical presentations, (2) a typical or atypical presentation along with objective test results that raise concern, or (3) atypical features, including equivocal test results, in patients with additional unreassuring findings (eg, systemic inflammation, hypotension, or altered mental status). The common approach to antibiotic administration targeting meningeal infection is presented in **Table 2**.

RESPIRATORY INFECTIONS

Upper Respiratory Infections

Sinusitis

Fever is a common presenting symptom associated with acute maxillary sinusitis. Fever can be present whether the infection is caused by a virus (commonly rhinovirus) or a bacterium (commonly *S pneumoniae* and *H influenzae*). Therefore, the presence of

| Risk Factors | Common Pathogens | Antimicrobial Therapy |
|-----------------------------------|--|--|
| <1 mo | <i>Streptococcus agalactiae</i> , <i>Escherichia coli</i> , <i>Listeria monocytogenes</i> , <i>Klebsiella</i> , herpes simplex virus, varicella zoster virus | Ampicillin ^a + cefotaxime; or ampicillin + aminoglycoside + acyclovir (as needed for viral suspicion) |
| 1–23 mo | <i>Streptococcus pneumoniae</i> , <i>Neisseria meningitidis</i> , <i>S agalactiae</i> , <i>Escherichia coli</i> , <i>Haemophilus influenzae</i> , herpes simplex virus, varicella zoster virus | Vancomycin + third-generation cephalosporin + acyclovir (as needed for viral suspicion) |
| 2–50 y | <i>S pneumoniae</i> , <i>N meningitidis</i> , herpes simplex virus, varicella zoster virus | Vancomycin + third-generation cephalosporin + acyclovir (as needed for viral suspicion) |
| >50 y | <i>S pneumoniae</i> , <i>N meningitidis</i> , <i>L monocytogenes</i> , aerobic gram-negative bacilli, herpes simplex virus, varicella zoster virus | Vancomycin + third-generation cephalosporin + ampicillin + acyclovir (as needed for viral suspicion) |
| Trauma: basilar skull fracture | <i>S pneumoniae</i> , <i>H influenzae</i> , group A β -hemolytic streptococci | Vancomycin + third-generation cephalosporin |
| Trauma: penetrating trauma | <i>Staphylococcus aureus</i> , coagulase-negative staphylococcus (ie, <i>Staphylococcus epidermidis</i>), aerobic gram-negative bacilli (including <i>Pseudomonas aeruginosa</i>) | Vancomycin + cefepime ^b or ceftazidime ^b or meropenem ^b |
| Following neurosurgery | <i>S aureus</i> , coagulase-negative staphylococci (ie, <i>S epidermidis</i>), aerobic gram-negative bacilli (including <i>P aeruginosa</i>) | Vancomycin + cefepime ^b or ceftazidime ^b or meropenem ^b |
| CSF shunt | <i>S aureus</i> , coagulase-negative staphylococci (ie, <i>S epidermidis</i>), aerobic gram-negative bacilli (including <i>P aeruginosa</i>), <i>Propionibacterium acnes</i> | Vancomycin + cefepime ^b or ceftazidime ^b or meropenem ^b |

^a Ampicillin is added to specifically target *L monocytogenes*.

^b Cefepime, ceftazidime, or meropenem is added to specifically target *P aeruginosa*.

Adapted from Tunkel AR, Hartman BJ, Kaplan SL, et al. Practice guidelines for the management of bacterial meningitis. Clin Infect Dis 2004;39:1267–84; with permission.

fever cannot be used to guide treatment. Most cases of acute rhinitis and sinusitis have a viral source and run a benign course. These facts, coupled with growing concern about bacterial resistance, have led the CDC to advise judicious use of antibiotics. Supportive care with decongestants should be sufficient to treat viral sinusitis.²²

Longer duration of symptoms suggests a bacterial source. A course of antibiotics might be advisable when symptoms last longer than 10 days, the patient is febrile with severe symptoms of pain and purulent discharge, or the patient has experienced resolution of the symptoms of an upper respiratory infection only for headache, facial pain, or purulent nasal discharge to return. These infections are commonly caused by *S pneumoniae* or *H influenzae*, for which β -lactam with β -lactamase inhibitor is indicated.

Increasing resistance over the previous decade emphasizes the importance of selecting antibiotics that are effective against β -lactamase-producing organisms. In patients who are allergic to penicillin, doxycycline (preferred) or a fluoroquinolone is recommended. Resistance to macrolides is now so widespread that they cannot be recommended as first-line therapy. Empiric coverage for MRSA is not recommended.²³

Pharyngitis

Adult pharyngitis is most frequently a viral infection, but adults, like children, remain susceptible to group A β -hemolytic streptococci. Gonococcal infection is a less common but nevertheless important cause of bacterial pharyngitis. Approximately 5% to 15% of cases of adult pharyngitis are secondary to group A streptococci and, of that group, 1 in 3000 is at risk for acute rheumatic fever.²⁴ The Centor criteria can usefully guide the diagnosis and treatment of acute pharyngitis:

1. History of fever
2. Absence of cough
3. Tonsillar exudates
4. Tender anterior cervical lymphadenopathy

When all 4 criteria are positive, patients should be treated empirically for GAS. Patients with 2 or more criteria should be tested with a rapid streptococcal antigen test. If this result is positive, the patient should be treated with penicillin (if the patient is allergic to penicillin, a macrolide may be used).²⁴

Acute bronchitis

Acute bronchitis is an acute respiratory illness characterized by cough, with or without sputum production, lasting up to 3 weeks.²⁵ As with other upper respiratory infections, 90% of cases are viral in origin. The most common culprits are influenza, parainfluenza, respiratory syncytial virus, and adenovirus. When bacteria are implicated, the most common organisms are *Bordetella pertussis*, *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae*.²⁶

Routine empiric treatment with antimicrobials is not recommended for acute bronchitis. However, when patients present within 48 hours after symptom onset and a polymerase chain reaction of a nasal swab confirms influenza A or B, a neuraminidase inhibitor (ie, oseltamivir or zanamivir) may decrease the severity and duration of symptoms, and is therefore useful in selected populations.

The CDC recommends initiation of antiviral treatment as soon as possible for patients in whom influenza is suspected or confirmed, and who are hospitalized, have severe, complicated underlying progressive illness, or are at risk for influenza complications. The following groups are considered at high risk for complications: those at the extremes of age (<2 years or >65 years); those with significant chronic pulmonary disease, neurologic disease, diabetes, or an immunocompromised state; women who are pregnant or in the postpartum period (within 2 weeks after delivery); those who are younger than 19 years and on long-term aspirin therapy; American Indians/Alaska Natives; the morbidly obese (body mass index ≥ 40 kg/m²); and residents of chronic care facilities.²⁷ The CDC no longer recommends treatment of influenza A with amantadine, because 100% of strains tested since 2008 were found to be resistant.

When a patient with apparent bronchitis experiences episodic worsening of the illness and has a persistent, high-pitched cough, the diagnosis of *B pertussis* should be entertained. For patients who have those characteristics and who either did not

receive the pertussis vaccine or received it more than 10 years previously, empiric treatment with macrolides can be considered. Trimethoprim-sulfamethoxazole may be administered to patients who are allergic to macrolides.

LOWER RESPIRATORY INFECTIONS

Community-Acquired Pneumonia

Pneumonia is the eighth leading cause of death in the United States.²⁸ Given its epidemiologic significance, research and policy priorities have focused on early recognition and treatment. In 2002, the Joint Commission on Accreditation of Healthcare Organizations and the Center for Medicare and Medicaid Services identified early antibiotic administration in pneumonia as a core performance measure.²⁹ The relevant literature suggests real but limited benefit from early antibiotic administration in community-acquired pneumonia (CAP); benefits from earlier treatment in patients with nosocomial infections (health care–associated pneumonia and ventilator-associated pneumonia) are significant and apparent.² Patients with CAP often present with typical features, including fever, cough, and an infiltrate on chest film. If the illness is particularly severe or if the patient is immunocompromised, the presentation can be dominated by nonspecific features such as altered mental status, and atypical findings such hypothermia or the absence of fever.

CAP can be bacterial or viral in origin. The most commonly implicated bacteria are *S pneumoniae*, *Mycoplasma pneumoniae*, *C pneumoniae*, *H influenzae*, *Legionella pneumophila*, anaerobes from aspiration, and gram-negative bacilli. Viral causes include influenza virus, parainfluenza virus, respiratory syncytial virus, human metapneumovirus, hantavirus, coronavirus, varicella, and rubeola.³⁰

The essential approach to suspected pneumonia requires estimation of its severity, including determination of whether inpatient or outpatient treatment is needed. The literature provides several prediction rules that may be helpful. The Pneumonia Severity Index (PSI), or PORT score, is one such commonly used tool.³¹ The PSI includes 20 markers, and could therefore prove cumbersome for application in many clinical settings.

Another commonly used prediction rule is the CURB-65 method, promoted by the British Thoracic Society. This tool is less complex than the PSI, so its application is more feasible in clinical settings.³² Each key element is given 1 point, as described:

- C: Confusion, defined as disorientation to place, time, or person or another finding that causes concern during examination of mental status
- U: Uremia, with blood urea nitrogen level higher than 7 mmol/L (20 mg/dL)
- R: Respiratory rate 30 breaths/min or more
- B: low Blood pressure (systolic <90 mm Hg or diastolic <60 mm Hg)
- 65: age 65 years or older.

The simplified recommendation is that patients with a total score of 0 or 1 can be treated on an outpatient basis, those with a score of 2 warrant admission to inpatient wards, and those with a score of 3 or more should be considered for care in the intensive care unit. No scoring system is sufficient to replace clinical judgment, but sufficient judgment might allow either of these tools to be useful in appropriately selected situations. In addition, the likely pathogens should be identified so that the appropriate spectrum of activity for antibiotic coverage can be determined. Toward this end, the American Thoracic Society (ATS) and the IDSA jointly published guidelines in 2007 (**Box 1**).³³

Box 1**Treatment of community-acquired pneumonia**

1. Outpatient treatment
 - a. Previously healthy with no prior antimicrobials within 3 months
 - i. Macrolide (unless in a region with high *Streptococcus pneumoniae* resistance)
 - ii. Doxycycline
 - b. Presence of chronic conditions and comorbidities or prior treatment with antimicrobial:
 - i. Respiratory fluoroquinolone (moxifloxacin, gemifloxacin, or levofloxacin)
 - ii. β -Lactam plus a macrolide
2. Inpatients, non-ICU treatment
 - a. Respiratory fluoroquinolone
 - b. β -Lactam plus a macrolide
3. Inpatients, ICU treatment
 - a. β -Lactam (third-generation cephalosporin or ampicillin-sulbactam) plus fluoroquinolone or macrolide
 - i. Penicillin allergic: fluoroquinolone plus aztreonam
 - b. Pseudomonal risk (recent hospitalization or structural lung disease)
 - i. Antipneumococcal/antipseudomonal β -lactam (piperacillin-tazobactam, cefepime, imipenem, or meropenem) plus fluoroquinolone (ciprofloxacin or levofloxacin)
 - ii. Or the above β -lactam plus aminoglycoside plus azithromycin or fluoroquinolone
 - iii. Penicillin allergic: aztreonam rather than above β -lactams
 - c. Community-acquired MRSA risk, add vancomycin or linezolid to the above regimens

Abbreviation: ICU, intensive care unit.

Adapted from Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2010: pelvic inflammatory disease. 2011. Available at: www.cdc.gov/std/treatment/2010/pid.htm. Accessed March 26, 2013.

Hospital-Acquired Pneumonia

The ATS and the IDSA divide hospital-acquired pneumonia into 2 categories: health care-associated pneumonia (HCAP) and ventilator-associated pneumonia (VAP). HCAP is a nosocomial infection acquired in an acute care hospital or a chronic care facility. VAP can occur in the acutely critically ill and in patients with chronic respiratory failure requiring mechanical ventilation. The most common multidrug-resistant gram-negative bacterial pathogen that causes hospital-acquired pneumonia is *P aeruginosa*. Other pathogens that should be considered are *K pneumoniae*, *Enterobacter*, *Serratia*, *Acinetobacter*, *Stenotrophomonas*, *Burkholderia cepacia*, MRSA, *S pneumoniae*, *H influenzae*, *Legionella*, *Candida*, *Aspergillus*, influenza, parainfluenza, adenovirus, measles, and respiratory syncytial virus.³⁴

Treatment decisions are based on the patient's risk profile for drug-resistant organisms. Patients at highest risk are those who have been in chronic care facilities, who frequent dialysis centers, who were hospitalized for 2 or more days in the previous 90 days, who live in communities with a high prevalence of resistance, who have a family member with a known resistant organism, or who are immunosuppressed (**Table 3**).³⁴

| | | | |
|---|--|--|------------------------------------|
| MDR/ <i>Pseudomonas</i> #1 ^a | Cephalosporin (cefepime or ceftazidime) OR | Carbapenem (imipenem or meropenem) OR | β-Lactam (piperacillin-tazobactam) |
| MDR/ <i>Pseudomonas</i> #2 ^a | Fluoroquinolone (ciprofloxacin or levofloxacin) OR | Aminoglycoside (amikacin, gentamicin, or tobramycin) | |
| MRSA | Linezolid OR | Vancomycin | |
| Legionella | Fluoroquinolone (ciprofloxacin or levofloxacin) OR | Azithromycin | |

If a pathogen is suspected, each should be treated with one antimicrobial from each row.

^a Given the increasing resistance patterns, multidrug-resistant (MDR) organisms/*Pseudomonas* should be covered with combination therapy and 2 antimicrobials (one from each row), in addition to coverage for MRSA and *Legionella*, if applicable.

Data from American Thoracic Society; Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med 2005;171:388–416.

As discussed earlier, when treating drug-resistant organisms it is imperative to understand local resistance patterns, to be aware of institutional recommendations based on in-house epidemiologic studies and antibiograms, and, most importantly, to consider resistant patterns documented in a specific patient's medical history.

Tuberculosis

Because of the public health implications surrounding tuberculosis (TB), clinicians should maintain a high index of suspicion toward their patients' risk for this disease. The CDC has delineated the following high-risk populations: the immunocompromised, the incarcerated, international travelers, and immigrants from countries with a high prevalence of TB.³⁵ High clinical suspicion for active TB in a patient being assessed in the ED warrants initiation of appropriate precautions and treatment. Because the prevalence of organisms resistant to isoniazid is so high, the World Health Organization recommends administration of 4 antimicrobials to patients suspected of having active TB for the first 2 months of treatment: ethambutol, isoniazid, rifampin, and pyrazinamide.³⁶

CARDIAC

Establishing the diagnosis of infective endocarditis is particularly challenging early in the course of illness. The Duke criteria should be useful in guiding the decision to begin empiric therapy in the ED (**Table 4**). This approach recommends initiation of treatment in the ED for cases that meet 2 major criteria, 1 major and 3 minor criteria, or 5 minor criteria.

Empiric therapy is not typically instituted unless the patient has become acutely ill and is exhibiting signs of sepsis. Before treatment is initiated, a serious effort to identify the infectious source should be undertaken. An appropriate blood culture is essential in this effort, using at least 3 samples from 3 sites, if possible. The most common offending organism is *S aureus*.

For patients with native valves, initial treatment with ampicillin-sulbactam combined with gentamicin is recommended in most cases. For patients who are allergic to

| Major Criteria | Minor Criteria |
|---|--|
| Blood culture positive: viridans streptococci, <i>Streptococcus bovis</i> , HACEK group, <i>Staphylococcus aureus</i> , enterococci OR persistently positive blood cultures OR a single positive blood culture for <i>Coxiella burnetii</i> or anti-phase 1 IgG antibody titer >1:800 | Predisposing heart condition or intravenous drug use |
| Echocardiogram positive for infective endocarditis (TEE is the most sensitive) | Fever >38°C |
| | Vascular phenomena; major arterial emboli, septic pulmonary infarcts, mycotic aneurysms, intracranial hemorrhage, conjunctival hemorrhage, Janeway lesions |
| | Immunologic phenomena: glomerulonephritis, Osler nodes, Roth spots, rheumatoid factor |
| | Blood culture positive that does not meet major criteria |

Abbreviations: HACEK, *Haemophilus*, *Actinobacillus*, *Cardiobacterium hominis*, *Eikenella corrodens*, *Kingella kingae*; IgG, immunoglobulin G; TEE, transesophageal echocardiography.

Adapted from Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications. *Circulation* 2005;111:e394-433; with permission.

penicillins, treatment with vancomycin combined with gentamicin and ciprofloxacin can be considered. When endocarditis develops in an intravenous drug abuser, the infective organism is usually *S aureus*; vancomycin is commonly recommended in this patient population. The clinician should remain alert to the possibility of polymicrobial infections in these patients.³⁷

Patients with prosthetic valves should receive broader coverage administered aggressively. Coverage of *Bartonella* species, in particular, should be ensured. Common recommendations are ceftriaxone with gentamicin with or without doxycycline. When patients are not actively symptomatic and their clinical condition remains stable, admission for further workup to establish the diagnosis definitively is recommended if endocarditis is suspected.³⁷

ABDOMINAL INFECTIONS

Intraluminal intestinal flora is the most common cause of intra-abdominal infection. The Surgical Infection Society and the IDSA jointly issued recommendations pertaining to patients with abdominal infections. When abdominal infection is suspected and signs of systemic inflammation or hypoperfusion are present, administration of antibiotics should begin empirically in parallel with efforts to definitively identify the source.³⁸ When an intra-abdominal source of infection is suspected, surgical consultation is necessary to plan the treatment course.

DIVERTICULITIS, APPENDICITIS, AND BOWEL ISCHEMIA

The most common microbial causes of abdominal infections are enteric gram-negative aerobic and facultative bacilli, and enteric gram-positive streptococci.

Antimicrobial treatment should include coverage for those organisms and, when the distal small bowel, appendix, or colon is involved, obligate anaerobic bacilli should also be covered. Current guidelines suggest that routine blood cultures tend to not be helpful. Blood cultures are more likely to be helpful when patients are exhibiting signs of sepsis or are immunocompromised, and when resistant organisms are suspected.³⁸ Standard recommendations for empiric coverage in adult patients with mild or moderate disease call for administration of cefoxitin, ertapenem, moxifloxacin, tigecycline, or ticarcillin–clavulanic acid. When the illness is judged to be severe or when the patient’s vulnerability is judged to be high (in someone at an advanced age or in an immunocompromised host), broader coverage is typically advisable.³⁸

Decisions regarding the treatment of nosocomial infections should be guided by culture data and local resistance patterns. Broad-spectrum antibiotics are typically needed. Treatment decisions must be adapted when uncommon sources are suspected; fungal infection (commonly *Candida albicans*) might require the addition of fluconazole, and resistant *Staphylococcus* species might require vancomycin or linezolid.³⁸

Diverticulitis is a relatively common abdominal infection that can be treated medically, and on an outpatient basis in selected cases. General recommendations suggest that uncomplicated cases (ie, patients with diverticulitis for the first time, those without bowel perforation or abscess formation, patients who can hydrate orally, and those who can achieve sufficient pain control) can be discharged with instructions to obtain outpatient treatment and follow-up. Oral treatment regimens should include moxifloxacin, ciprofloxacin plus metronidazole, levofloxacin plus metronidazole, or amoxicillin–clavulanic acid.³⁸

BILIARY INFECTIONS

The organisms that typically cause acute cholecystitis and acute cholangitis are slightly different from those associated with other intra-abdominal infections. Antimicrobial therapy does not need to cover anaerobes unless a biliary-enteric anastomosis is present. An enterococcal infection should be considered if the patient has received an organ transplant or is otherwise immunocompromised. Therefore, targeted organisms usually include enteric gram-negative aerobic and facultative bacilli, and enteric gram-positive streptococci (**Table 5**).

Special Case: Diarrhea

Diarrhea is a common complaint among ED patients. Most cases pose little risk to life or health, but diarrheal illness causes significant discomfort and distress. When diarrhea is profuse and persistent, the patient faces the risk of dehydration and hypovolemia. Most patients require only supportive care. Some require rehydration (either orally or intravenously). Antimicrobial therapy should be reserved for patients with fever or hemorrhagic features.³⁹

When antimicrobial therapy is contemplated, the decision to obtain targeted stool studies should be made in tandem. Determining which stool studies are needed is linked to clinical suspicion. If an inflammatory cause is possible, a stool sample should be examined for fecal polymorphonuclear leukocytes. If the patient is hemorrhagic and a shiga-toxin–producing *Escherichia coli* (*E coli* O157) is suspected, a test specific for that organism can be requested.³⁹ In patients with community-acquired or traveler’s diarrhea, infection secondary to *Salmonella*, *Shigella*, *Campylobacter*, *E coli* O157:H7, or *Clostridium difficile* should be considered.

| Infection | Regimen |
|---|--|
| Community-acquired acute cholecystitis of mild to moderate severity | First-, second-, or third-generation cephalosporin (cefazolin, cefuroxime, or ceftriaxone) |
| Community-acquired acute cholecystitis with toxic appearance, shock, advanced age, or immunocompromised condition | Carbapenems, piperacillin-tazobactam, levofloxacin, cefepime, COMBINED WITH metronidazole |
| Acute cholangitis following bilioenteric anastomosis of any severity | Carbapenems, piperacillin-tazobactam, levofloxacin, cefepime, COMBINED WITH metronidazole |
| Health care-associated biliary infection of any severity | Carbapenems, piperacillin-tazobactam, levofloxacin, cefepime, COMBINED WITH metronidazole AND vancomycin |

Data from Solomkin JS, Mazuski JE, Bradley JS, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infection Diseases Society of America. *Clin Infect Dis* 2010;50:133–64.

Diarrhea secondary to *Salmonella* and *Shigella* should be treated with fluoroquinolones in adults and trimethoprim-sulfamethoxazole in children. *Campylobacter* has increasing antimicrobial resistance, and should be treated with a macrolide. *E coli* O157 should be suspected in patients who are afebrile but have hemorrhagic diarrhea. Given the significant risk of hemolytic uremic syndrome from shiga-toxin release, diarrhea suspected to be secondary to *E coli* O157 should not be treated with antimicrobial therapy. Supportive care alone is recommended. *C difficile* should be considered in immunosuppressed patients with acute diarrhea and in those who have been recently treated with antimicrobials for another infection. Initial therapy should include oral metronidazole.³⁹

When diarrhea begins after a recent hospitalization, infection with *C difficile* should be considered.³⁹ When diarrhea persists for more than 7 days, parasitic infections or other inflammatory processes should be considered.

PELVIC INFECTIONS

Genitourinary Infections

Uncomplicated urinary tract infections

In 2010 the IDSA, in conjunction with the American Congress of Obstetricians and Gynecologists, the American Urological Society, the Association of Medical Microbiology and Infectious Disease—Canada, and the Society for Academic Emergency Medicine, updated guidelines for the treatment of uncomplicated cystitis and pyelonephritis in otherwise healthy premenopausal women.⁴⁰ In otherwise young healthy patients, uncomplicated cystitis is not usually associated with fever. However, if a patient with urinary tract symptoms has a fever or complains of back pain, pyelonephritis or complicated urinary tract infection (UTI) should be considered.

When treating cystitis, community and hospital antibiograms should be reviewed. The vast majority of UTIs in the community are caused by *E coli*; the remainder is caused by other gram-negative pathogens, including *Proteus mirabilis* and *K pneumoniae*, or gram-positive *Staphylococcus saprophyticus*. Resistance patterns in communities change frequently. Following the best practices and recommendations in one's community ensures the best targeting of treatment. If a local antibiogram is not

available, the IDSA guidelines can be followed (**Box 2**). These guidelines state that, in some communities, resistance is so common that community-specific resistance data really are necessary for the treatment of UTIs.

Complicated urinary tract infections

Pyelonephritis Pyelonephritis should be considered in patients with symptoms of cystitis paired with systemic symptoms of fever, malaise, and flank or back pain. Treatment should be targeted to the specific pathogen; therefore, cultures are generally advisable. As for the treatment of uncomplicated cystitis, empiric antibiotics should be chosen based on local resistance patterns.

When treating empirically, several options are available. In areas where the local resistance is less than 10%, fluoroquinolones are commonly recommended for outpatient treatment.⁸ The current guidelines recommend oral ciprofloxacin, 500 mg 2 times a day for 7 days.⁴⁰ If the resistance exceeds 10% or if the patient has an intolerance or hypersensitivity to quinolones, trimethoprim-sulfamethoxazole can be used for outpatient therapy. When admission is necessary, intravenous antibiotics are recommended, typically a third-generation quinolone.

Catheter-associated urinary tract infection Catheterized patients are at risk of infection secondary to different microbes compared with typical UTIs. In general, the patient remains at risk for the typical organisms but are also at increased risk of *staphylococcus* and *streptococcal* infections given the instrumentation of the urethral tract. Unfortunately, some of the typical symptoms that concern providers for UTI may not be appreciated in patients with catheters. For example, urgency, frequency and dysuria will not be present. Therefore, one must have a high index of suspicion in a patient with a catheter and proceed systematically to reach the diagnosis.

In patients with suspected catheter associated infections, if unable to simply remove the Foley and attempt a trial of void to obtain a sample, the catheter should be removed and replaced. The cultures should then be sent from the new catheter.⁴¹ The ideal is to treat a positive urine culture. However, as frequently mentioned in this

Box 2

Treatment algorithm for uncomplicated UTI in otherwise healthy young females

1. Initial treatment options^a
 - a. Nitrofurantoin/monohydrate, 100 mg twice daily for 5 days
 - b. Trimethoprim-sulfamethoxazole, 160/800 mg (double-strength tablet) twice daily for 3 days
2. If the patient cannot tolerate the initial treatment options or if the initial treatment failed, consider the following^b:
 - a. Fluoroquinolone
 - b. β -Lactam
 - c. First-generation cephalosporins

^a Do not use in patients who might have early pyelonephritis.

^b These options are less desirable because of the resistance they can induce and because of population effects.

Data from Gupta K, Hooton TM, Naber KG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: a 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clin Infect Dis 2011;52(5):e103–20.

review, cultures are less than ideal in the emergency department. The urine leukocyte count, presence of nitrites, and urine appearance and odor may help direct clinical suspicion.

Treatment should be targeted at the possible infecting organisms. Because chronically ill populations often have chronic indwelling catheters, the prior culture data from the patient's chart should be reviewed if available. The prevalence of the resistant organisms and fungal infections is much greater in this population, and if that prior data is available in the ED it should be used to help direct treatment.⁴¹ Otherwise, as discussed above, treatment should focus on the organisms that are at risk for infecting the patient and be relatively broad in coverage to cover gram positive, gram negative and anaerobic organisms.

Prostatitis Acute bacterial prostatitis frequently presents with concomitant UTI: hematuria, dysuria, frequency, suprapubic or rectal pain, etc, however, it is extremely important to try differentiate between a simple UTI and an associated prostatitis. In general, otherwise healthy men have minimal risk for a UTI. Although acute bacterial prostatitis is uncommon, the overall prevalence of prostatitis is high and estimated at approximately 9.7% of males.^{42,43} If acute bacterial prostatitis is suspected, it is imperative that emergency physicians start appropriate treatment as the incidence of recurrence with progression to chronic bacterial prostatitis is extremely high and estimated at 20–50%.⁴³ Initial treatment should seek to optimize clearance of the offending organism in hopes of decreasing the potential for recurrence. Duration of treatment is often four weeks, so if discharged home, the patient should have prompt primary care follow up.

As mentioned above, the prostate is an organ with relatively limited blood flow. Therefore, penetration of antibiotics can be difficult and an agent that is bactericidal should be used. The most common microbes are *E coli* (87.5%), *Pseudomonas*, *Proteus*, *Klebsiella*, and polymicrobial infections.⁴⁴ Therefore, antibiotics should target these gram negative organisms. The most highly recommended agent is levofloxacin.^{42,44} It has significant gram negative coverage, is bactericidal, and is renally excreted while also withstanding the low pH of the prostate and can therefore reach desired levels in prostatic tissue (see **Table 1**). Other agents that may be considered in the setting of hypersensitivity to fluoroquinolones include aminoglycosides with or without a penicillin like ampicillin, or a third-generation cephalosporin with or without an aminoglycoside.⁴⁵ Patients who have been instrumented or are immunocompromised may be at risk of different organisms and should be covered more broadly to ensure sufficient coverage of gram-positive organism like *S Aureus*, including addressing the possibility of resistant organisms.

Gynecologic Infections

The presence of fever in the setting of a gynecologic infection is relatively rare; however, infection of the gynecologic tract is relatively common. Given the increasing resistance of *Neisseria gonorrhoeae*, attention to antibiotic coverage updates is important. The CDC has liberalized its recommendations regarding the treatment of pelvic inflammatory disease (PID) in an effort to improve control.

The presentation of PID can range from pelvic pain with minimal tenderness to fever, a toxic appearance, and shock. Although fever is the focus of this discussion, it is imperative to stress that pelvic pain in a young sexually active female without a clear cause should raise suspicion for PID. PID includes all infections of the upper gynecologic tract: endometritis, salpingitis, and tubo-ovarian abscess.

Treatment of PID (mild to severe) should be directed at *N gonorrhoeae*, *Chlamydia trachomatis*, and anaerobes such as *Bacteroides fragilis*. Regimens are dependent on the severity of the illness. Treatment of sexual partners is advised (Table 6).⁴⁶ Pregnant patients with suspected PID should be hospitalized and receive parenteral antibiotics.

SKIN AND SOFT-TISSUE INFECTIONS

The management of skin and soft-tissue infections can pose diagnostic challenges. In particular, acute infection superimposed on chronic changes associated with wounds or venous stasis might not always be easily detected.⁴⁷ Severe cases manifest with systemic signs, including fever, and should be easier to detect. Once systemic manifestations occur, intravenous antibiotics are needed; surgical treatment might also be necessary. IDSA guidelines emphasize the importance of key signs consistent with severe cases, including pain disproportionate to examination findings, violaceous bullae, cutaneous hemorrhage, skin sloughing, anesthesia, rapid progression, and gas in the tissue.⁴⁷

Cellulitis

Cellulitis is most commonly caused by gram-positive organisms. Streptococci (most often group A β -hemolytic streptococci) and staphylococci are the most prevalent causes of soft-tissue infections in otherwise healthy individuals. The approach to distinguishing staphylococcal from streptococcal cellulitis is based on clinical findings. *S aureus* is often associated with furuncles, carbuncles, and abscesses. When cellulitis is not associated with a clear portal of entry and diffuse erythema is found, *Streptococcus* species are more likely. Blood cultures are not routinely useful.⁴⁷

Simple cellulitis should be treated empirically with a penicillinase-resistant penicillin or a first-generation cephalosporin. Penicillin-allergic patients should be treated with clindamycin or vancomycin when inpatient treatment is required. The prevalence of community-acquired MRSA is increasing across the United States. In settings where prevalence is high, the threshold to cover should be low. Clindamycin, trimethoprim-sulfamethoxazole, and tetracyclines are effective for community-acquired MRSA. In

| Severity | Regimen |
|---|---|
| Mild PID | Ceftriaxone, 250 mg IM single dose, PLUS doxycycline, 100 mg PO BID for 14 d, PLUS metronidazole, ^a 500 mg PO BID for 14 d Alternative: ceftriaxone, 250 mg IM single dose, PLUS azithromycin, 1 g PO once a week for 2 wk, PLUS metronidazole, ^a 500 mg PO BID for 14 d |
| Moderate to severe PID, or with tuboovarian abscess | Cefotetan, 2 g IV every 12 h, OR cefoxitin, 2 g IV every 6 h, PLUS doxycycline, 100 mg IV every 12 h Alternative: clindamycin, 900 mg IV every 8 h, PLUS gentamicin (varied dosing recommendations) |

Abbreviations: BID, twice daily; IM, intramuscular; IV, intravenous; PO, by mouth.

^a Metronidazole is recommended for concomitant treatment of bacterial vaginosis (a single 2-g dose of metronidazole can also be considered).

Adapted from Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2010: pelvic inflammatory disease. 2011. Available at: www.cdc.gov/std/treatment/2010/pid.htm. Accessed March 26, 2013.

inpatient settings, vancomycin remains the antimicrobial of choice although other options do show promise, including linezolid, daptomycin, and tigecycline.^{48,49}

Necrotizing Infections

Emergency physicians should maintain a high index of suspicion for necrotizing infections. Features that should engender concern include pain out of proportion to appearance, skin necrosis, crepitus or gas detected on imaging, bullae, skin sloughing, marked edema or firmness of subcutaneous tissue extending beyond erythema, cutaneous anesthesia, rapid progression, and evidence of sepsis.⁴⁷ Necrotizing infections can develop in any patient, but those with vascular insufficiency are at heightened risk (eg, diabetics and patients with venous stasis, lymphedema, or peripheral vascular disease). Antibiotic therapy is required. Emergency surgical source control is the cornerstone of therapy.

These infections can be caused by a single organism (eg, *Streptococcus pyogenes*, *Vibrio vulnificans*, *Aeromonas hydrophila*, or MRSA), but polymicrobial infections are more common. Patients with penetrating trauma and a concomitant reduction in blood flow are at increased risk for gas gangrene, a particularly worrisome polymicrobial infection often caused by *Clostridium* species.⁴⁷

Broad-spectrum antibiotics, covering gram-positive organisms, gram-negative organisms, aerobes, and anaerobes, are required. The current treatment recommendation for mixed infections indicates penicillin with β -lactamase inhibition combined with clindamycin and ciprofloxacin.

Fournier gangrene should be considered in patients with perineal cellulitis/necrotizing fasciitis, with perianal or complex UTI, or with a history of trauma that may have allowed the entry of bacteria into the genital fascial planes.⁴⁷ Aggressive intravenous administration of antibiotics, specifically covering *Pseudomonas*, is required. Debridement is the definitive treatment.

SUMMARY

The choice and timing of antimicrobial therapy are challenging for the acute care physician. The resistance that antimicrobials have developed to certain pathogens has changed the emergency physician's approach to patients and the process by which priorities are determined. The role of emergency physicians as stewards of health care resources is growing. In all cases, an organized approach to evaluation, diagnosis, and treatment is helpful. Using antimicrobials rationally means ensuring that the right treatments are available to the right people at the right time and in the right place.

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