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REVIEW-NARRATIVE CME

The Top 10 Infectious Disease Pitfalls That Hospitalists Can Avoid

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Infectious diseases are commonly encountered by hospitalists in their day-to-day care of patients. Challenges involved in caring for patients with infectious diseases include choosing the correct antibiotic, treating patients with a penicillin allergy, interpreting blood cultures, and caring for patients with human immunodeficiency virus (HIV). The evidence-based pearls in this article will help hospitalists avoid common pitfalls in the recognition and treatment of such disorders and guide their decision about when to consult an infectious diseases specialist. ***Journal of Hospital Medicine*** **2010;5:42–45.** © *2010 Society of Hospital Medicine.*

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Hospitalists commonly encounter the challenges of infectious diseases in their hospitalized patients. Choosing the correct antibiotic, interpreting blood cultures, working up causes of fever, treating patients with an allergy to penicillin, and caring for patients with human immunodeficiency virus (HIV) commonly confront the hospitalist. This article presents evidence-based pearls which will help hospitalists avoid common infectious disease pitfalls and guide their decision about when to consult an infectious diseases specialist.

1. Avoid ''Spiraling Empiricism'' and Understand Common Fallacies in Prescribing Empiric Antimicrobial Therapy

The term ''spiraling empiricism'' describes the ''inappropriate treatment, or the unjustifiable escalation of treatment, of suspected but undocumented infectious diseases.''[1] Initiation of carefully considered empiric broad-spectrum antibiotic therapy for an acutely ill patient is an entirely appropriate and reasonable strategy. But all too often, practitioners are confronted with clinical dilemmas such as persistent fever or lack of response to therapy. In these circumstances, clinicians are faced with deciding whether to add or change antibiotics to broaden coverage. Changes in empiric therapy should be made sparingly, and only when there is new information or symptoms to justify an addition or change. In order to make an accurate assessment of response, steady-state levels should be achieved and usually 3 to 5 days should be allowed to pass. Lack of response to broad-spectrum therapy should trigger further investigation for occult infection or consideration of noninfectious etiologies and not simply the addition of a new antimicrobial agent. If a microbial pathogen is isolated from a blood culture(s) or other relevant source, antimicrobials should be tailored to the narrowest spectrum and least toxic therapy based on the sensitivities of that organism. For critically ill patients or patients who do not appear to be improving, an infectious diseases consultation may be warranted.

2. Know the Important Drug-Drug Interactions Between Antimicrobials and Commonly-used Inpatient Medications, Particularly With Those Involving Warfarin

Most antimicrobials (especially antifungals, quinolones, metronidazole, and sulfonamides) can cause unpredictable elevations in the international normalized ratio (INR) concurrent with warfarin administration, either through inhibition of warfarin metabolism or alterations in vitamin K–producing gut flora. When using antimicrobials in patients on warfarin, the patient's INR should be carefully monitored and adjustment of the warfarin dose may be necessary. Antimicrobials that are inhibitors of cytochrome P-450 enzymes include ciprofloxacin, levofloxacin, isoniazid, fluconazole, and clarithromycin. In contrast, rifampin is a potent inducer of most known cytochrome P-450 enzymes and increases the metabolism of many drugs used in patients in the hospital setting, including anticonvulsants, beta-blockers, calcium channel blockers, and other antibiotics like fluoroquinolones, and sulfonylureas. Moreover, the concurrent oral intake of tablets or solutions (including tube feeds) with a high concentration of trivalent and divalent cations (such as aluminum, magnesium, and, to a lesser extent, calcium, iron, and zinc) impairs gastrointestinal absorption of fluoroquinolones and should be avoided or spaced apart in time. Since fluoroquinolones can potentially prolong the QT interval, careful monitoring is necessary when a patient is

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prescribed other QT prolonging agents. Finally, many antimicrobials reduce the effectiveness of oral or other systemic hormonal contraceptives and patients should be routinely advised to use nonhormonal methods of birth control during therapy.

3. Positive Blood Cultures for Bacteria or Fungus Should be Repeated Serially Every 24 to 48 Hours Until the Cultures Are Negative

An important step in the management of a positive blood culture for bacteria or yeast is to check follow-up blood cultures every 24 to 48 hours until the bacteremia or fungemia has cleared. This is particularly true of bacteremia caused by *Staphylococcus aureus (S. aureus)*, *Enterococcus* species, and fungemia caused by *Candida* species. The duration of bacteremia or fungemia has a significant impact on the predictive values of further testing for endovascular or deep-seated sources of infection as well as treatment duration. This is particularly true for the treatment of candidemia in nonneutropenic adults and for bacterial endocarditis, in which the recommended duration of treatment starts from the day of the last positive blood culture.[2,3] In addition to repeat blood cultures, a blood culture positive for *S. aureus* should always prompt an aggressive workup for a source (including strong consideration of a transesophageal echocardiogram to evaluate for endocarditis). *S. aureus* bacteremia should never be disregarded as a contaminant, and should prompt strong consideration of removal of all indwelling intravenous lines.[4]

4. Removal of Indwelling Intravascular Catheters Is Essential in the Management of Patients with Candidemia. In These Patients, Retention of Central Lines Is Significantly Related to Poor Outcomes

In patients with culture-proven *Candida* fungemia, all intravascular catheters must be removed if at all possible. In a study by Nguyen et al.,[5] the mortality rate for patients with a catheter-related candidemia in whom catheters were retained was significantly higher than that of patients in whom the catheters were removed (41% vs. 21%, $P < 0.001$). Likewise, in a separate study, Luzzati et al.[6] noted that central line removal independently reduced the high mortality of the disease. This recommendation applies to all *Candida* species.

5. Although *Candida* Species Are Frequently Noted to Colonize Sputum and Urine Cultures, Their Recovery From Multiple Sites May Be an Indicator of Occult Candidemia in an Acutely Ill Patient

Candida species uncommonly cause pneumonia or urinary tract infection, so their isolation from cultures of the respiratory and genitourinary tract often represents colonization. However, the presence of *Candida* species at multiple sites may be an indicator of occult candidemia in a patient with multiple risk factors for candidemia, including intensive care unit (ICU) admission, immunosuppression (particularly neutropenia and recent receipt of corticosteroids), central venous catheterization, total parenteral nutrition, recent broad-spectrum antibiotics, and recent abdominal or gastrointestinal surgery.[7]

6. Patients with Asymptomatic Bacteriuria, With or Without Pyuria, Should Not Be Treated with Antibiotics. Pregnant Women and Patients Undergoing a Genitourinary Procedure Are the Exception and Should Be Treated With Antibiotics

Asymptomatic bacteriuria is commonly encountered in the hospital setting, but is usually benign. Bacteriuria is defined as a voided urine specimen with 1 bacterial species isolated in a quantitative count of $\geq 10^5$ cfu/mL. Treatment of asymptomatic bacteriuria is only recommended for pregnant women or prior to invasive genitourinary procedures, including transurethral resection of the prostate. Patients with structural or functional abnormalities of the urinary tract may have a high prevalence of bacteriuria. Despite its prevalence, asymptomatic bacteriuria is seldom associated with adverse outcomes. Studies have noted that antimicrobial treatment of asymptomatic bacteriuria does not decrease recurrence. Negative outcomes with antimicrobial treatment do occur, including adverse drug reactions and reinfection with organisms of increasing resistance. Clinical trials in spinal-cord injury patients, diabetic women, elderly patients living in the community or nursing home, and patients with indwelling urethral catheters have consistently found no benefit with treatment of asymptomatic bacteriuria.[8,9] The presence or absence of pyuria does not differentiate symptomatic from asymptomatic urinary infection. Patients with symptomatic urinary tract infection (fever and/or dysuria) should be treated after urine cultures are obtained. Other causes of pyuria in the absence of an acute urinary tract infection include urethritis, tuberculosis, prostatitis, nephrolithiasis, and malignancy.

7. Evaluate All Patients Who Have a History of Penicillin Allergy and Consider Desensitization for Patients With a History Consistent With Immunoglobulin E–mediated Allergy Who Require Treatment With a Beta-Lactam Antibiotic

Patients commonly claim to have an allergy to penicillin. True penicillin allergy is very serious and can be life-threatening. Because of this, patients labeled as "penicillin allergic" are typically not treated with beta-lactam antibiotics. Instead, they may be prescribed medications which are typically less effective, more toxic, have a broader spectrum, or are more expensive.[10,11] Many patients are inappropriately labeled as having a penicillin allergy. A history of penicillin allergy is reported in approximately 10% of hospitalized patients, but only approximately 10% of those who report a history of penicillin allergy actually have an allergic reaction when treated with penicillin. Exanthems are frequently associated with beta-lactam use during an episode of infectious

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mononucleosis but these are not considered an allergic reaction. Such patients are generally able to tolerate beta-lactams subsequent to this episode. Nonpruritic maculopapular rashes are also reported in 3% to 7% of children taking amoxicillin and are not a contraindication for future beta-lactam or cephalosporin use.[12] All patients who describe an allergy should be questioned in detail about the type of penicillin received, as well as the type, severity, and timing of the reaction. Typical immunoglobulin E (IgE)-mediated severe reactions to penicillin include urticaria, pruritus, angioedema, bronchospasm, and hypotension. These patients should not be given other agents that share the same beta-lactam ring, including cephalosporins (risk of cross-reactivity is greatest with first-generation and second-generation cephalosporins). Carbapenems have minimal cross-reactivity, particularly meropenem.[13] Monobactams (eg, aztreonam) do not cross-react. While skin testing to penicillin can be considered in patients with a history of a severe reaction to penicillin, neither the major nor minor determinants are commercially available at this time. In patients with a history of a possible IgE-mediated reaction and when there is no suitable alternative antibiotic (usually determined from infectious diseases consultation), desensitization to beta-lactams or carbapenems can be considered. Desensitization should be reserved only for clinicians experienced with these techniques, preferably in consultation with a specialist in allergy and immunology. Patients who report a non-IgE-mediated reaction may be prescribed a cephalosporin if necessary (preferably a third-generation or fourth-generation).[14]

8. An Abrupt Increase in Leukocytosis In a Hospitalized Patient Should Prompt Consideration of *Clostridium difficile* Infection

In recent years, there has been a marked increase in the incidence and severity of *Clostridium difficile* (*C. difficile*) infection (CDI). A new hypervirulent strain, NAP1/BI/027, has emerged and is becoming endemic in the United States, Canada, and Europe. Typically *C. difficile* causes diarrhea, abdominal pain, and fever. Often patients have received antibiotics in the recent past, placing them at higher risk, but cases can occur sporadically (even in the community setting) or be transmitted nosocomially. Early detection appears to be essential in reducing the serious morbidity and mortality associated with this disease. Observational studies suggested that *C. difficile* infection is a common cause of unexplained leukocytosis or a sudden worsening of preexisting leukocytosis.[15,16] In a prospective study evaluating 60 patients with unexplained leukocytosis (white blood cell count $\geq$15,000/mm^3), 58% of patients with leukocytosis in the absence of localizing symptoms and signs of infection were subsequently diagnosed with CDI. The authors believe that the percent may have been as high as 73% when they included patients with a negative toxin assay who rapidly responded to metronidazole therapy.[17] White blood cell counts can range from 10,000 to 20,000/mm^3 in moderate disease. Counts as high as 40,000/mm^3 can occur, especially in patients with severe disease. Although the use of clindamycin and cephalosporins have been classically associated with the subsequent development of CDI, the current widespread use of fluoroquinolones has led to significant fluoroquinolone resistance among strains of *C. difficile*, especially the hypervirulent NAP1/BI/027 strain.[18] The judicious use of antibiotics, especially fluoroquinolones, remains the cornerstone in preventing CDI. Remember that hand washing with soap and water is essential as alcohol-based hand sanitizers do not eradicate the *C. difficile* spores. The drug of choice for initial treatment of mild to moderate CDI remains oral metronidazole, and it may be used for a first recurrence of CDI. Increasing data support the use of oral vancomycin for moderately severe to severe CDI or for multiple recurrences.[19] Intravenous metronidazole is often added to oral vancomycin in patients with ileus, but it is not reliably effective alone for CDI.

9. Fever Is Common in the First 48 Hours After a Major Surgical Procedure, and Is a Poor Indicator of Infection. The use of Antibiotics in Response to Fever in the Absence of Other Localizing Signs and Symptoms of Infection Should Be Avoided

Early postoperative fever is relatively common but most fevers that develop within the first 48 hours after surgery do not have an infectious etiology.[20–23] However, fever that begins or persists beyond the fifth postoperative day is much more likely to represent a clinically significant infection. The continued use of antibiotics outside the window for wound prophylaxis (>24 hours) does not decrease the risk of postoperative infection but it does increase the risk of acquiring resistant bacteria and adverse drug reactions, including CDI.

10. Facts All Clinicians Should Know About Patients with HIV Infection

The 2 most common laboratory abnormalities routinely associated with antiretroviral therapy for HIV infection are unconjugated hyperbilirubinemia associated with atazanavir and an elevated mean corpuscular volume (MCV) associated with zidovudine (and, to a lesser extent, stavudine). Immune reconstitution inflammatory syndrome (IRIS) is a condition seen in patients with advanced acquired immune deficiency syndrome (AIDS) who have recently started antiretroviral therapy. As the immune system begins to recover, it may respond to a previously acquired opportunistic infection with an overwhelming inflammatory response that paradoxically makes the symptoms of infection worse. IRIS is associated with a pathological inflammatory response that can have substantial morbidity and mortality.[24] For this reason, when considering whether to start or stop continuous or highly active antiretroviral therapy (also known as HAART), an infectious diseases consult is recommended. *Pneumocystis jiroveci* (PCP) remains a cause of pneumonia

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in patients with advanced AIDS' though in the era of HAART, its presentation may be more subtle. Finally, the principle of parsimony (Occam's razor) often does not hold in the diagnosis of opportunistic infections in patients with advanced AIDS, as these patients can often present with multiple infections simultaneously.[25,26]

Conclusion

Infectious diseases are commonly encountered by physicians who care for hospitalized patients. Early recognition, evaluation, and appropriate treatment and/or referral to an infectious diseases specialist are necessary to moderate the significant morbidity and mortality that are often associated with infectious diseases.

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