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REVIEWS

Empiric Antibiotic Selection Strategies for Healthcare-Associated Pneumonia, Intra-Abdominal Infections, and Catheter-Associated Bacteremia

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Initial selection and early deployment of appropriate/adequate empiric antimicrobial therapy is critical to minimize the significant morbidity and mortality associated with hospital- or healthcare-associated infections (HAIs). Initial empiric therapy that inadequately covers the pathogen(s) causing a serious HAI has been associated with increased mortality, longer hospital stay, and elevated healthcare costs. Moreover, subsequent modification of initial inadequate therapy, later in the disease process when culture results become available, may not remedy the impact of the initial choice. Because of this, it is important that initial empiric therapy covers the most likely pathogens associated with infection in a particular patient, even if this initial regimen turns out to be unnecessarily broad, based on subsequent culture results. The current paradigm for management of serious HAIs is to initiate empiric therapy with a broad-spectrum regimen covering likely pathogens, based on local surveillance and susceptibility data, and presence of risk factors for involvement of a resistant microorganism. Subsequent modification (de-escalation) of the initial regimen becomes possible later, when culture results are available and clinical status can be better assessed, 2 to 4 days after initiation of empiric therapy. When possible, de-escalation and other steps to modify antimicrobial exposure are important for minimizing risk of antimicrobial resistance development. This article examines the general process for selection of initial empiric antibiotic therapy for patients with HAIs, illustrated through 3 case studies dealing with healthcare-associated pneumonia, complicated intra-abdominal infection, and catheter-associated bacteremia, respectively. *Journal of Hospital Medicine* 2012;7:S2–S12.

Early appropriate antimicrobial therapy is necessary to minimize the morbidity and mortality associated with hospital- or healthcare-associated infections (HAIs). A number of studies have demonstrated that delayed or inadequate antimicrobial therapy leads to worse clinical outcomes and higher healthcare costs.[1,2] Inadequate antimicrobial therapy can also promote or enhance the development of resistance,[2] with potential wide-ranging impact beyond the immediate patient under care. Because delaying treatment until availability of culture results decreases the likelihood of a successful outcome, patients with a suspected invasive HAI commonly receive empiric therapy with a regimen expected to cover the most likely causative pathogens. Based on characteristics of the patient and healthcare facility or unit, likely pathogens may include bacteria or other pathogens resistant to 1 or more antimicrobial drug classes. This article discusses the various processes and factors that need to be considered when choosing empiric antibiotics in the hospital or other healthcare setting, and uses 3 case studies dealing with pneumonia, intra-abdominal infection, and bacteremia, respectively, to illustrate points of interest.

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IMPORTANCE OF EARLY ADEQUATE ANTIBIOTIC USE

The initial selection and early deployment of adequate antimicrobial therapy is critical for successful resolution of HAIs. The terms inadequate and inappropriate antimicrobial therapy are commonly used interchangeably in the literature, and can be defined as "use of antimicrobial treatment without (sufficient) activity against the identified pathogen."[2] Using an antibiotic for a fungal infection would be inadequate, as would using a drug or dosing regimen that is ineffective against the identified bacterial species due to resistance or a failure to achieve the drug's pharmacokinetic/pharmacodynamic target for efficacy against the pathogen. The complete absence of antimicrobial therapy is also considered inadequate therapy. Some investigators consider inappropriate therapy a more general term that includes excessive treatment as well as inadequate treatment.[1] Others reserve the term inappropriate for use of an antimicrobial without activity against the identified pathogen, and the term inadequate for use of an insufficient regimen, either in terms of optimal dose, route of administration, timeliness, or failure to use combination therapy when appropriate.[3] However, many or most research

articles do not make the distinction, and the current article does not make a distinction.

In addition, some articles arbitrarily define inadequate therapy as either use (or absence) of a treatment without activity against the identified pathogen *or* a delay in appropriate or adequate treatment, eg, no patient exposure to adequate treatment within 24 hours of hospital admission. It is important to recognize this when evaluating articles in the literature. Other studies separate inadequate and delayed therapy as variables. However, when dealing with empiric therapy, the adequacy of initial empiric therapy cannot be fully determined until subsequent possession of the tissue/blood culture results.

Inadequate Antibiotic Treatment

A 1999 study by Kollef et al. identified inadequate antimicrobial treatment as the most important independent predictor of hospital mortality, in a group of patients with a nosocomial or community-acquired infection, while in the medical or surgical intensive care unit (ICU).[4] Infection sites included in the study were lung, bloodstream, urinary tract, gastrointestinal (GI) tract, and wound. Various other studies have confirmed an association between inadequate antibiotic therapy and increased hospital mortality, and some demonstrated a relationship between inadequate antibiotic therapy and longer hospital or ICU stays[5–7] and higher hospital-related costs.[8] More specifically, initial inappropriate antibiotic therapy has been associated with increased mortality in patients with healthcare-associated[9] or ventilator-associated pneumonia (VAP)[5,7,8,10–14] and those with bacteremia/sepsis.[6,10,15–24] Inadequate empiric therapy has also been linked with worsened outcomes,[19,25–29] longer hospital stays,[25–27,29] and increased healthcare costs[25,29] in patients with infections of the GI tract.

With respect to specific bacterial pathogens, inappropriate antibiotic therapy has been shown to increase risk of hospital mortality for patients with VAP or bacteremia caused by *Pseudomonas aeruginosa*,[20,30] extended-spectrum β-lactamase (ESBL)-producing or multidrug-resistant (MDR) *Klebsiella pneumoniae* or *Escherichia coli*,[21,31,32] and methicillin-resistant *Staphylococcus aureus* (MRSA).[15,23] In fact, infection with resistant bacteria, and particularly MDR bacteria, is a principal risk factor for inadequate initial antibiotic therapy.[14,16,33,34] A recent study by Teixeira and coworkers showed that inadequate therapy was more than twice as common for additional episodes of VAP caused by MDR pathogens as for those involving drug-susceptible pathogens (56% vs 25.5%).[14] Moreover, VAP caused by MDR pathogens was identified as a significant independent predictor of inadequate antimicrobial therapy (odds ratio [OR], 3.07; 95% confidence interval [CI], 1.29-7.30; $P = 0.01$). Infections caused by drug-resistant versus susceptible bacteria have generally been associated with increased morbidity, longer hospital or ICU stays, and higher costs.[24,34–37] At least part of the reason for these worsened outcomes appears to be an increased likelihood that initial therapy is inadequate for the causative agent. Because of this, it is particularly important to consider the probability of infection with resistant bacteria when initiating empiric antibiotic therapy.

Delayed Antibiotic Treatment

In addition to inadequate initial therapy, a delay in the onset of adequate therapy has also been shown to have negative impact on outcome in patients with VAP, bacteremia, or intra-abdominal infections.[12,13,27,38,39] For example, Iregui et al. identified administration of initially delayed appropriate antibiotic treatment (treatment delayed for ≥24 hours after initial diagnosis of VAP) as a significant predictor of hospital mortality (OR, 7.68; 95% CI, 4.50-13.09; $P < 0.001$) in patients with VAP at a US teaching hospital.[38] Similarly, Lodise et al. identified delayed antibiotic treatment as an independent predictor of infection-related mortality in patients with hospital-acquired *S aureus* bacteremia (OR, 3.8; 95% CI, 1.3-11.0; $P = 0.01$).[39] Delayed versus early antibiotic therapy was also associated with significantly longer hospital stay (20.2 vs 14.3 days, $P = 0.05$). Classification and regression tree analysis identified 44.75 hours from the initial positive blood culture result to appropriate therapy as the breakpoint between delayed and early treatment for bacteremia.

Of particular interest, evidence suggests that the negative impact of initial delay or initial use of inadequate therapy often cannot be remedied by subsequent treatment alterations. For example, Luna et al. reported a significantly lower hospital mortality rate for VAP patients who received early adequate antibiotic therapy compared with those who received early inadequate therapy (38% vs 91%, $P < 0.001$).[13] In this study, "early" treatment referred to drug administration prior to bronchoscopy, which was performed within 24 hours of clinical diagnosis of VAP. A subset of patients only received treatment after bronchoscopy, and the mortality rate for VAP-positive patients who received adequate antibiotic therapy after this initial delay was similar to that for VAP-positive patients who received inadequate therapy postbronchoscopy (71% vs 70%). In other words, the negative impact of an initial delay in adequate therapy could not be subsequently overcome by using adequate antibiotic therapy later in the disease process. Similarly, a recent study by Zilberberg et al. of healthcare-associated pneumonia reported that the negative effect of initial inadequate antibiotic therapy on hospital mortality could not be mitigated by subsequent escalation of adequate antibiotic therapy after reception of culture results.[9] Finally, a study of inadequate initial empiric antibiotic therapy of postoperative intra-abdominal infection (peritonitis) also showed that

adverse outcomes could not be abrogated by changes in antibiotic therapy based on culture results.[27] Taken together, the results from these studies emphasize the importance of early adequate antibiotic therapy.

PRACTICAL GUIDELINES FOR CHOOSING EMPIRIC ANTIBIOTICS

When choosing initial empiric therapy for a suspected hospital- or healthcare-related bacterial infection, it is first important to determine if the patient has received prior antibiotic therapy, and if the patient has, then the clinician should consider choosing an antibiotic from a different drug class. This is because prior antibiotic therapy increases risk of infection with a pathogen resistant to the initial antibiotic drug and other members of its class. Also, depending on the site of the infection and likely pathogenic bacteria, the clinician will need to decide whether to initiate empiric therapy with a single antibiotic or combination of agents. A number of patient- and institution-related factors can be utilized by clinicians to better identify the likely pathogen responsible for the infection, and it is critical to use this information when selecting initial empiric therapy. Finally, as is true whenever choosing antimicrobial or other drug therapies, clinicians need to consider and weigh the safety/tolerability profile, potential for drug–drug interactions, and relative cost of different treatment options. These will vary for individual patients receiving the same drug or drug combination.

MINIMIZING ANTIMICROBIAL RESISTANCE IN THE HOSPITAL OR HEALTHCARE SETTING

It is also important to consider the potential for development of antibiotic resistance when choosing initial empiric therapy. The current paradigm for treatment of serious hospital or healthcare infections is to prescribe broad-spectrum antimicrobial therapy upfront while awaiting culture results, and to de-escalate (or terminate) therapy once culture results are available[40–42]—or as 2 authors recently put it, ''get it right the first time, hit hard up front, and use large doses of broad-spectrum antibiotics for a short period.''[41] The initial empiric antibiotic regimen should have a high likelihood of covering the most likely causative pathogens, including resistant species or strains. Furthermore, emergence of resistance is minimized when the initial regimen effectively covers the most likely causative pathogens, and subsequent culture results are utilized to streamline or narrow the initial regimen, when possible.[40,42] Emergence of resistance is also minimized by using the shortest duration of treatment with maximal clinical effect. (These latter 2 points are discussed in greater detail in the Kaye and File articles in this supplement.)

Factoring in Institution- and Patient-Specific Factors

Local antibiograms are useful in determining the most likely infection-causing pathogens, within different wards of the hospital, and their susceptibility or resistance to various antibiotics. Local patterns of pathogen susceptibility and resistance can differ markedly from national averages, so local antibiograms are more useful than national or even regional surveillance data when making choices about the initial agent and dosing regimen for initial empiric therapy.[43] Hospitals are required by the Joint Commission to create antibiograms on at least an annual basis, although more frequent antibiograms are particularly useful, given that susceptibility or resistance patterns change over time. It is also important that hospital microbiologists create antibiograms specifically for different hospital wards or departments, as well as hospital-wide. The incidence and susceptibility of pathogenic bacteria has been shown to vary across different wards within a hospital, as well as within different regions of a given country.[44–46]

Patient-specific factors should also be considered in the decision-making process for selection of initial empiric therapy for a suspected bacterial infection. Relevant patient characteristics or factors may differ somewhat when examining risk for particular types of infection (eg, healthcare/hospital-acquired pneumonia, VAP, or bacteremia) or particular antibiotic-resistant pathogens (eg, MRSA, ESBL-producing *E coli* or *Klebsiella* spp, *P aeruginosa* and MDR *P aeruginosa*, and carbapenem-resistant *Acinetobacter baumannii*). Nonetheless, several risk factors appear to generally increase risk of infection with a resistant pathogen across these subcategories, including prior antibiotic treatment (with agents sometimes varying depending on the particular pathogen of interest); recent hospital admission or residence in a nursing home or extended-care facility; prolonged hospital stay (particularly in the ICU); prior colonization with the pathogen; presence of an indwelling catheter (central venous, arterial, or urinary); and mechanical ventilation; among others.[2,47,48] Patients who are immunocompromised, either due to their condition or immunosuppressive therapy, are also generally at increased risk of infection with resistant bacteria.[47]

Patient age and presence of comorbidities can also affect initial selection of empiric therapy. Cell-mediated immunity tends to decline with age, and elderly individuals are also more likely to have conditions or comorbidities associated with diminished host immunity, both of which may contribute to increased susceptibility to infection and infection involving resistant bacteria.[49] Furthermore, elderly individuals are more likely to have decline in renal or hepatic function or other physiologic changes that can alter drug pharmacokinetics and pharmacodynamics,[50] and these factors need to be considered when selecting an initial empiric

therapy regimen that covers likely pathogens, without increasing risk of drug toxicity. In addition, the increased number of comorbidities in elderly patients typically translates into polypharmacy, with potential for drug–drug interactions that need to be weighed when selecting initial empiric therapy.

Treat Infection, Not Contamination or Colonization

It is important to limit antimicrobial use to treatment of actual infections, and not for treatment of colonization or contamination. Treatment of colonization is a significant source of antimicrobial overuse. Hence, it is important that healthcare teams take appropriate steps to ensure they are treating pneumonia, bacteremia, or a urinary tract infection, not colonization of the tracheal aspirate, catheter tip or hub, or indwelling urinary catheter that is unassociated with actual infection. Strategies to employ when considering how to differentiate between true infection and colonization include using Gram stain in sputum specimens to look for evidence of polymorphonuclear leukocytes (inflammation), understanding that certain organisms, such as *Enterococcus* and *Candida* are not respiratory pathogens, recognizing that urinary catheters may be colonized in the absence of infection, and remaining vigilant regarding blood culture contamination. Since antibiotic use is generally linked to increased risk of resistance,[51,52] antibiotics should only be used when there is a clear clinical benefit associated with their use; treatment of colonization does not fit this description. When in doubt, an infectious diseases (ID) specialist consultation is recommended.

Similarly, overuse/misuse of antibiotics that occurs due to false-positive culture results also increases development of resistance in hospitalized patients. In particular, contamination of blood cultures is relatively common in hospitalized patients, particularly in hospital emergency rooms,[53] and frequently results in administration of antibiotics to treat an apparent ''infection'' that actually represents a contaminated culture. Antimicrobial treatment due to false-positive blood culture results has been associated with prolonged hospitalization and elevated laboratory and hospital costs,[54,55] and provides an environment for development of antimicrobial resistance. Contamination of blood cultures often occurs at the point of blood collection via venipuncture or through indwelling catheters,[56,57] but can occur later in the process during laboratory handling or processing of specimens.[58] Hence, it is important to use proper antisepsis when collecting blood or other cultures, to make sure it is blood and not skin or the catheter hub that is being cultured, and to make sure to use proper methods when processing all cultures.

Consult Infectious Diseases Experts

The 2007 guidelines from the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America (IDSA/SHEA) for the development of institutional antimicrobial stewardship programs recommend inclusion of an ID physician and a clinical pharmacist with ID training as core members of a multidisciplinary antimicrobial stewardship team.[59] Consultation with an ID expert or inclusion of an ID specialist into an institutional antimicrobial stewardship program has been shown to improve antibiotic usage and reduce morbidity and mortality, length of hospital stay, healthcare costs, and resistance.[60–64] In hospitals without easy access to an ID specialist, hospitalists with ID training may be able to fulfill the role provided by ID physicians or clinical pharmacists with ID training.

TABLE 1. Key Initial Data for Case 1

History	A 72-yr-old woman recently hospitalized for congestive heart failure (CHF), returns to the emergency department from rehab with cough, fever, chills, shortness of breath, all progressively worsening over the past 36 hr
	Past history of CHF (ejection fraction 44%), myocardial infarction 2 yr ago, hypertension, past smoking
	Medications: metoprolol 50 mg BID; furosemide 40 mg daily; aspirin 81 mg daily; enalapril 20 mg daily
Physical	Vitals: BP 148/88, P 82, RR 16, T 101.7, O_2 sat 92% on room air
	Heart: S1, S2 no murmurs
	Lungs: crackles at R lung base
	Abdomen: bowel sounds present, non-tender
	Extremities: trace edema bilaterally
	Neurologic: no focal findings
Labs	EKG: NSR, no acute ST-T changes
	Chemistry, hemoglobin, platelets, within normal limits
	WBC: 14,700/mm^3, 10% bands
	Cardiac enzymes negative
	β-Natriuretic peptide within normal limits for age
	Chest X-ray: right lower lung infiltrate

Abbreviations: BP, blood pressure; EKG, electrocardiogram; NSR, normal sinus rhythm; P, pulse; R, right; RR, respiratory rate; sat, saturation; T, temperature; WBC, white blood cells.

CASE 1: HEALTHCARE-ASSOCIATED PNEUMONIA

Table 1 provides the key initial data for Case 1. The patient has a history of hypertension, congestive heart failure (CHF), and myocardial infarction (MI), and is receiving medications consistent with such a history. In terms of her acute presentation, cough, fever, chills, dyspnea, lung crackles (rales), X-ray evidence of lung infiltrate, reduced oxygen saturation, elevated white blood cell (WBC) count, and increased percentage of WBC bands are all consistent with a diagnosis of pneumonia of relatively recent origin. Progressive worsening of symptoms within the previous 36 hours is also consistent with infection of recent origin. There are no neurologic symptoms, and cardiac function appears relatively normal, with no evidence of MI or cardiac arrhythmia based on electrocardiogram or heart rate, although there is evidence of continuing hypertension and perhaps CHF.

Given the patient's history of recent hospitalization, the clinician should consider that the pneumonia is most likely hospital- or healthcare-acquired. Because

she was described as developing the problem while in rehabilitation, it can be assumed that hospitalization occurred relatively recently. Hospital-acquired pneumonia (HAP) is defined as pneumonia that occurs within 48 hours of hospital admission, and that was not incubating at the time of admission.[47,65] HAP accounts for approximately of 15% of all nosocomial/hospital-acquired infections in the United States and up to 27% in the ICU,[65,66] and is a frequent cause of morbidity and mortality in this setting.[65] In addition to hospitalization, other characteristics or risk factors for HAP include severe illness, hemodynamic compromise, depressed immune function, use of nasogastric tubes, and mechanical ventilation for the important subset of HAP patients with VAP.[65] VAP is more precisely defined as HAP that arises >48-72 hours after endotracheal intubation.[47]

Healthcare-associated pneumonia (HCAP) is a more recently defined category that includes patients with HAP and VAP, and is characterized by hospitalization for ≥2 days in the preceding 90 days, or residence in a nursing home or extended-care facility.[47,67,68] Additional risk factors for HCAP include intravenous therapy at home (including antibiotics); intravenous chemotherapy or wound care within 30 days of the current infection; and recent attendance at a hospital or hemodialysis clinic.[47] Most HAP or HCAP data have been derived from patients with VAP, and the 2005 American Thoracic Society (ATS)/IDSA guidelines for management of HAP, VAP, and HCAP recommend similar approaches for the initial treatment of patients with nonintubated HAP, VAP, and HCAP.[47] There are general similarities between these 3 disease categories with respect to etiology, epidemiology of likely pathogens, and prognosis, and important differences compared with community-acquired pneumonia (CAP), which in turn gives rise to different treatment strategies for HAP/VAP/HCAP and CAP.

Given an initial diagnosis of HAP or HCAP, the clinician should be considering the following questions: 1) What are the appropriate choices of antimicrobials? 2) What are the clinical parameters that should alert one to resistant organisms? 3) What are the appropriate cultures to order? 4) What is the role of Gram stain, if any?

Selection of Initial Empiric Therapy for Likely Pathogens

HAP is usually caused by bacterial pathogens, and much more rarely involves viruses or fungi in immunocompetent patients. Therefore, from the start, the focus should be on empiric therapy with an antibiotic or combination of antibiotics that has a high probability of covering the most likely pathogens. Empiric therapy is warranted because of the risk of mortality or other negative consequences when antibiotic therapy is delayed, particularly in an aged patient with a chronic illness like CHF (such as the case study here). Clues as to likely pathogens—and hence most appropriate antibiotic regimen—can be discerned by looking at the onset of HAP/VAP (early vs late) and whether the patient has risk factors for infection with a MDR or antibiotic-susceptible bacterial pathogen. A significant proportion of patients with HAP, VAP, or HCAP are infected with MDR pathogens, and identifying these patients and providing them with appropriate broad-spectrum empiric therapy is a key to successful management.

Early-onset HAP/VAP (occurring <5 days after hospitalization) is more likely to be due to antibiotic-sensitive bacteria than late-onset HAP/VAP (occurring ≥5 days after hospitalization), which often occurs due to MDR species.[47,69,70] Not surprisingly, risk of inappropriate initial antibiotic therapy[14] is higher, and mortality is also higher in patients with late-onset HAP/VAP.[47,71] Patients with early-onset HAP/VAP who have received prior antibiotics or been hospitalized within the past 90 days are also at risk for infection due to MDR bacteria, and hence should be treated the same as patients with late-onset HAP/VAP.[47] Additional risk factors for infection with MDR pathogens include antimicrobial therapy in the preceding 90 days (particularly with broad-spectrum agents), current hospitalization ≥5 days, high prevalence of antibiotic resistance in the specific hospital unit, immunosuppression, and presence of risk factors for HCAP (hospitalization ≥2 days in the preceding 90 days, residence in a nursing home or extended-care facility, home infusion therapy, chronic dialysis within 30 days, home wound care, or family member with MDR pathogen).[47] For VAP patients, duration of ventilator support ≥7 days is an additional risk factor for infection with a MDR pathogen.[70,72] A second episode of VAP is more likely to be due either to MRSA or *P aeruginosa*; therefore, these organisms need to be considered when selecting initial empiric therapy.

The most common bacterial causes of HAP, VAP, or HCAP include aerobic Gram-negative bacilli, such as *P aeruginosa*, *Acinetobacter* spp, and Enterobacteriaceae (eg, *K pneumoniae*, *E coli*, *Enterobacter* spp), and Gram-positive cocci, such as *S aureus* and *Streptococcus pneumoniae*.[47,73] MDR bacterial species are more likely when certain risk factors are present, and the ATS/IDSA guidelines recommend using a risk-stratification process when selecting empiric antibiotic therapy for patients with suspected HAP, VAP, or HCAP.[47] The guidelines also emphasize that local conditions can greatly impact whether a patient is infected with an antibiotic-sensitive or antibiotic-resistant species, regardless of other risk factors, thereby highlighting the importance of using recent hospital and hospital unit-specific antibiograms when stratifying a patient based on risk.

Other guiding principles of initial empiric treatment, as outlined in the ATS/IDSA guidelines, include not delaying therapy while awaiting culture results and

TABLE 2. Initial Empiric Antibiotic Therapy for HAP or VAP in Patients With No Known Risk Factors for MDR Pathogens, Early-Onset Disease, and Any Disease Severity

Potential Pathogen	Recommended Antibiotic
*Streptococcus pneumoniae**	
Haemophilus influenzae	Ceftriaxone
Methicillin-sensitive *Staphylococcus aureus*	*or*
Antibiotic-sensitive enteric Gram-negative bacilli	Levofloxacin, moxifloxacin, or ciprofloxacin
Escherichia coli	*or*
Klebsiella pneumoniae	Ampicillin/sulbactam
Enterobacter spp	*or*
Proteus spp	Ertapenem
Serratia marcescens	

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Abbreviations: HAP, hospital-acquired pneumonia; MDR, multidrug-resistant; VAP, ventilator-associated pneumonia.

*The frequency of penicillin-resistant *S pneumoniae* and MDR *S pneumoniae* is increasing; levofloxacin or moxifloxacin are preferred to ciprofloxacin, and the role of other quinolones, such as gatifloxacin, has not been established.

TABLE 3. Initial Empiric Antibiotic Therapy for HAP, VAP, or HCAP in Patients With Late-Onset Disease or Risk Factors for MDR Pathogens and All Disease Severity

Potential Pathogen	Combination Antibiotic Therapy
Pathogens listed in Table 2, plus MDR pathogens	Antipseudomonal cephalosporin (cefepime, ceftazidime)
Pseudomonas aeruginosa	*or*
Klebsiella pneumoniae (ESBL-positive)*	Antipseudomonal carbapenem (imipenem or meropenem)
Acinetobacter spp*	*or*
	β-Lactam/β-lactamase inhibitor (piperacillin-tazobactam)
	plus
	Antipseudomonal fluoroquinolone* (ciprofloxacin or levofloxacin)
	or
	Aminoglycoside (amikacin, gentamicin, or tobramycin)
	plus
Methicillin-resistant *Staphylococcus aureus* (MRSA)	Linezolid or vancomycin†
*Legionella pneumophila**	

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Abbreviations: ESBL, extended-spectrum β-lactamase; HAP, hospital-acquired pneumonia; HCAP, healthcare-associated pneumonia; MDR, multidrug-resistant; VAP, ventilator-associated pneumonia.

* If an ESBL-positive strain, such as *K pneumoniae*, or an *Acinetobacter* spp is suspected, a carbapenem is a reliable choice. If *L pneumophila* is suspected, the combination antibiotic regimen should include a macrolide (eg, azithromycin), or a fluoroquinolone (eg, ciprofloxacin or levofloxacin) should be used rather than an aminoglycoside.

† If MRSA risk factors are present or if there is high incidence locally.

administration of therapy as soon as possible following diagnosis; making sure the dosing regimen as well as drug selection is appropriate/adequate for the patient and suspected pathogen; and using a different class of antibiotic for patients with prior antibiotic exposure.[47] The guidelines further indicate that combination therapy is appropriate initial therapy in patients at high risk for infection with MDR bacteria, and that for patients receiving combination therapy including an aminoglycoside, the aminoglycoside can be stopped after 5-7 days in responding patients. Table 2 highlights ATS/IDSA recommendations for initial empiric antibiotic therapy in patients with suspected HAP/VAP who have early-onset disease and no risk factors for MDR pathogens.[47] Table 3 highlights recommendations for initial empiric antibiotic therapy in patients with suspected HAP/VAP/HCAP who have late-onset disease and/or risk factors for MDR pathogens.[47]

Returning to Case 1, given a clinical diagnosis of HAP/HCAP and the patient's heightened risk for infection with MRSA or resistant Gram-negative bacteria, she was initiated on a regimen consisting of piperacillin/tazobactam plus vancomycin and ciprofloxacin. The choice of 3 agents is consistent with ATS and IDSA guidelines to cover the potential for an ESBL-producer or *Acinetobacter*, or *Pseudomonas*. Individual choices should be dictated by one's own institutional antibiogram or some knowledge of the rehabilitation facility from which the patient was transferred.

Guiding Principles for Culture Management

Culture collection and management plays an important role in diagnosis and subsequent treatment of HAP/VAP or HCAP. As outlined in the ATS/IDSA guidelines, patient management typically proceeds using either a clinical strategy or bacteriologic strategy, or a combination thereof.[47] The clinical strategy makes use of cultures of endotracheal aspirates or sputum, with initial microscopic examination and Gram staining to identify bacterial growth and guide initiation of empiric antibiotic therapy. Cultures should always be performed before instituting antibiotic therapy. Microorganism growth is described as light, moderate, or heavy by microbiology laboratories using semiquantitative analysis. Gram staining should be performed only if the specimen is of good quality; most microbiology laboratories will do screening tests to ensure they are of good quality, or else will reject the specimen. When correlated with culture results, Gram staining can improve diagnostic accuracy.[74]

The bacteriologic strategy uses quantitative means to analyze and describe cultures of lower respiratory secretions or specimens obtained via endotracheal aspirates, mini-bronchoalveolar lavage specimens (mini-BAL), bronchoalveolar lavage, or protected-specimen bronchial brushing, collected with or without a bronchoscope, ie, with or without invasive techniques. Hence, whereas the clinical strategy uses noninvasive tracheal aspirates to culture microorganisms for analysis, the bacteriologic strategy often employs a relatively noninvasive strategy like a mini-BAL, or invasive (bronchoscopic) lower respiratory tract samples for quantitative culture analysis. Diagnosis of HAP/VAP or HCAP, and determination of

the causative microorganism(s), requires growth above a certain threshold when using the semi-quantitative analysis. The clinical approach is more sensitive, but can result in overtreatment, while the bacteriologic strategy is associated with risk of undertreatment due to false-negative culture results. On the other hand, quantitative cultures increase the specificity of diagnosis.

CASE 2: INTRA-ABDOMINAL INFECTION (DIVERTICULITIS)

Case 2 is a 56-year-old woman with no past medical history of note, who presented to her physician about 3 days ago, after 5 days of abdominal pain and fever (101.7°F). She had an outpatient computed tomography (CT) scan, and the results suggested diverticulitis. After the CT scan, she was given amoxicillin/clavulanate. She now presents to the emergency department (3 days later) with worsening pain, fever, and severe weakness. A physical exam shows low blood pressure (84/58 mmHg) and tachycardia (132 bpm). Her respiratory rate is 22 breaths per minute. Oxygenation (O_2 saturation 99% on room air) is normal, and the patient's lungs are clear. Abdominal examination reveals bowel sounds and diffuse tenderness, particularly at the left lower quadrant, and there is evidence of guarding and rebound. Her blood chemistry is generally normal, although the WBC count is elevated (15,200/mm^3). No abnormalities are evident on chest X-ray. The patient's blood pressure increases to 96/64 mmHg after she is infused with 2 liters of normal saline. She undergoes another CT scan and is admitted to the ICU. The CT scan shows diverticulitis with abscess and walled-off perforation. An interventional radiologist inserts a pigtail catheter into the abscess for sample collection, and the samples are sent to the microbiology laboratory for culture.

The radiology results indicate that the patient has what may be considered a complicated intra-abdominal infection (diverticulitis with abscess), community-acquired. Because empiric therapy is usually necessary for patients with complicated or even uncomplicated intra-abdominal infections, the clinician should now be asking: What is optimal empiric antimicrobial therapy for this patient? Both prior[75] and current guidelines[76] for the management of intra-abdominal infection indicate that antimicrobial therapy should be initiated when a patient receives such a diagnosis or when such an infection is considered likely. In making the determination of initial empiric therapy, the clinician should also be considering whether there is likely involvement of resistant Gram-negative bacteria, and if so, how that would change the choice of antibiotic therapy.

Enteric Gram-negative bacilli such as *E coli* and *K pneumoniae* are the most common microorganisms isolated from patients with intra-abdominal infections, although Gram-positive cocci (*Staphylococcus* or *Streptococcus* spp, and less commonly, enterococci) and obligate anaerobic organisms (particularly, *Bacteroides fragilis*) are also frequent components of intra-abdominal infections.[77] The relative frequency of bacterial pathogens shifts in patients who acquired their intra-abdominal infection in the hospital versus community setting, with greater prevalence of *Enterobacter*, *P aeruginosa*, and *Enterococcus* spp, and less frequent isolation of *E coli* and streptococci.[77] Recent results from the Study for Monitoring Antimicrobial Resistance Trends (SMART) indicate a general increase in resistance among Gram-negative bacilli isolated from patients with intra-abdominal infections treated in medical centers, primarily due to acquisition of ESBLs.[78,79] This is true both in the United States[79] and worldwide.[78] Carbapenems continue to exhibit consistent activity against Gram-negative bacilli isolated from intra-abdominal infections, including ESBL-producers.

Selection of initial empiric therapy should incorporate information from the literature and local antibiograms to determine the most likely causative pathogen(s), including ones with reduced susceptibility or resistance to commonly employed antibiotics. Then an antibiotic regimen should be selected that provides coverage of likely pathogens with minimal adverse events, including risk of collateral damage such as *Clostridium difficile*-associated disease. Dose and dosing interval considerations are also important, particularly in patients with reduced renal or hepatic function. The general approach is to select an antibiotic or combination of antibiotic agents to provide coverage of the bacterial pathogens most commonly isolated from patients with intra-abdominal infections, ie, aerobic/facultative anaerobic Gram-negative bacilli, aerobic Gram-positive cocci, and obligate anaerobic organisms.[77] Table 4 presents the antibiotic treatment recommendations from the Surgical Infection Society and IDSA 2010 guidelines for management of patients with complicated intra-abdominal infections.[76] The guidelines are based on whether the patient has mild-to-moderate or high-risk/severe community-acquired complicated intra-abdominal infections. Recommendations for the empiric treatment of hospital or healthcare-associated complicated intra-abdominal infections are largely based on local antibiogram (microbiologic) results, and include some similarities and differences compared with recommended treatment of high-risk community-acquired infections, as illustrated in Table 5.[76] A patient with mild-to-moderate infection would be someone who does not require intensive care, and has community-acquired intra-abdominal infection due to secondary peritonitis. Severe intra-abdominal infection would be defined by requiring intensive care, having sepsis, or having healthcare-acquired peritonitis (such as a bowel leak following surgery). In line with these guidelines, and considering the case patient's risk profile, ciprofloxacin plus metronidazole was selected as initial empiric therapy,

TABLE 4. Antibiotic Agents and Regimens That May Be Used for the Initial Empiric Treatment of Extra-Biliary Complicated Intra-Abdominal Infection

	Community-Acquired Infection in Adults	
Regimen	Mild-to-Moderate Severity*	High Risk or Severity†
Single agent	Cefoxitin, ertapenem, moxifloxacin, tigecycline, and ticarcillin-clavulanate	Imipenem-cilastatin, meropenem, doripenem, and piperacillin-tazobactam
Combination	Cefazolin, cefuroxime, ceftriaxone, cefotaxime, ciprofloxacin, or levofloxacin, each in combination with metronidazole‡	Cefepime, ceftazidime, ciprofloxacin, or levofloxacin, each in combination with metronidazole‡

NOTE: Adapted from Solomkin et al.[76]
* Perforated or abscessed appendicitis and other infections of mild-to-moderate severity.
† Severe physiologic disturbance, advanced age, or immunocompromised state.
‡ Because of increasing resistance of *Escherichia coli* to fluoroquinolones, local population susceptibility profiles and, if available, isolate susceptibility should be reviewed.

TABLE 5. Recommendations for Empiric Antibiotic Therapy for Hospital or Healthcare-Associated Complicated Intra-Abdominal Infection

	Regimen				
Organisms Seen in the Hospital/Healthcare Infection at the Local Institution	Carbapenem*	Piperacillin-Tazobactam	Ceftazidime or Cefepime + Metronidazole	Aminoglycoside	Vancomycin
<20% Resistant *Pseudomonas aeruginosa*, ESBL-producing Enterobacteriaceae, *Acinetobacter*, or other multidrug-resistant Gram-negative bacteria	Recommended	Recommended	Recommended	Not recommended	Not recommended
ESBL-producing Enterobacteriaceae	Recommended	Recommended	Not recommended	Recommended	Not recommended
P aeruginosa >20% resistant to ceftazidime	Recommended	Recommended	Not recommended	Recommended	Not recommended
Methicillin-resistant *Staphylococcus aureus*	Not recommended	Not recommended	Not recommended	Not recommended	Recommended

NOTE: Reproduced from Solomkin et al.[76] "Recommended" indicates that the listed agent or class is recommended for empiric use, before culture and susceptibility data are available, at institutions that encounter these isolates from other hospital or healthcare-associated infections. These may be unit- or hospital-specific.
Abbreviations: ESBL, extended-spectrum β-lactamase.
* Imipenem-cilastatin, meropenem, or doripenem.

because she had not been hospitalized previously. Although she was hypotensive, the blood pressure was easily raised with fluids.

There are a number of controversies in intra-abdominal sepsis management. These include whether or when initial empiric therapy should provide coverage of *Enterococcus*/vancomycin-resistant enterococci or MRSA, when the regimen should include an antifungal to cover possible *Candida* spp infection, the role of resistant *Bacteroides* in intra-abdominal infections, and when clinicians should be particularly concerned about ESBL-producing or other resistant Gram-negative bacteria. These topics are beyond the reach of the present article, but are and will continue to be important issues for clinicians to grapple with when selecting initial empiric therapy for patients with intra-abdominal infections.

CASE 3: CENTRAL LINE-ASSOCIATED BACTEREMIA

The third case is a 56-year-old man with epilepsy who presents to the emergency department with status epilepticus. Subsequent resuscitative efforts included intubation and placement of an internal jugular central line. The patient was admitted to the ICU, and aggressive treatment was initiated with repeated intravenous dosing of lorazepam and loading with fosphenytoin, which successfully broke the seizure. Subsequent imaging and laboratory tests failed to reveal any specific cause for the status epilepticus. The patient was extubated on day 4 and transferred out of the ICU. On day 5, he spiked a fever of 103.4°F. He did not report any new symptoms, and there was no evidence of cough, sputum, shortness of breath, abdominal pain, diarrhea, or urinary symptoms. Physical examination revealed normal blood pressure (122/68 mmHg) and oxygen saturation (95% on room air), a normal respiratory rate (12 breaths per minute), clear lungs, no edema, no heart murmur, and normal neurologic findings. The patient's heart rate was somewhat high (102 bpm), and his temperature remained elevated (103.4°F). Abdominal examination revealed no tenderness, and bowel sounds were present. Laboratory results were normal, except for an elevated WBC count (17,000/mm^3 of blood). The chest X-ray was clear.

This is an example of a patient with fever and leukocytosis of unknown origin. There are no focal findings indicative of a particular infection site or process. The patient was treated in the ICU, including use of a central catheter. Differential diagnosis of fever and leukocytosis without source, in a patient from the ICU with a central line, should consider catheter-associated bacteremia; *C difficile*-associated disease; a silent intra-abdominal process, such as cholangitis or gangrenous cholecystitis; drug fever related to (in this patient) anticonvulsant therapy; urinary tract infection (no evidence for in this patient); or pulmonary embolism. The clinician needs to make a decision as to the

relative benefits of empiric antibiotic or other antimicrobial treatment versus observation. If the patient is to be treated with an antibiotic, then a choice has to be made as to the best agent for the patient at hand.

In terms of the choice of antibiotics for a patient such as the one here, the clinician needs to assess the severity of illness and, when doing so, determine what infection site or sites should be covered, and the most likely sites of infection. A determination of likely pathogens also needs to be made. Cultures should be obtained prior to initiating therapy with a regimen providing broad coverage of the most likely pathogen(s), while allowing for the possibility of later de-escalation based on clinical evaluation and culture results. This is similar to the situation for initial empiric treatment of pneumonia or intra-abdominal infection. In general, the clinician should obtain blood, urine, and possibly sputum cultures to aid in future decision making. Furthermore, if the patient has diarrhea (which the current one does not), the clinician should obtain a stool for *C difficile* toxin analysis.

For the case illustrated here, the clinician determined catheter-associated bacteremia was a strong possibility, and decided to initiate empiric therapy with vancomycin and piperacillin-tazobactam to provide coverage of MRSA and resistant Gram-negative bacteria. The most common causes of nosocomial or catheter-associated bloodstream infections (BSIs) are coagulase-negative staphylococci, *S aureus*, enterococci, and *Candida* spp,[80–82] but Gram-negative bacilli like *P aeruginosa*, *Klebsiella* spp, and *E coli* (among others) are also frequently involved, particularly in patients with catheter-associated BSIs.[81] Moreover, significant and increasing percentages of Gram-negative bacilli exhibit resistance to 1 or more antibiotic classes,[83–85] and >50% of *S aureus* are typically MRSA,[82,83,85,86] although there has been some decline in MRSA central line-associated BSIs in US ICUs in recent years.[87]

Clinical practice guidelines from the IDSA recommend vancomycin (or daptomycin) for the management of MRSA bacteremia,[88] while piperacillin-tazobactam is frequently empirically added to Gram-positive coverage for serious hospital-acquired infections because of its broad activity against many pathogenic bacteria, including some ESBL-producing Gram-negative bacteria and *P aeruginosa*,[89] which are significant causes of patient morbidity and mortality.[36,90] However, to be effective, both vancomycin and piperacillin-tazobactam need to be properly dosed to maximize their pharmacodynamic properties. Guidelines from the American Society of Health-System Pharmacists, IDSA, and Society of Infectious Diseases Pharmacists recommend vancomycin serum trough concentrations of 15-20 mg/L for patients with bacteremia due to MRSA.[91] These levels are recommended to improve penetration, increase the probability of obtaining optimal target serum concentrations, and improve clinical outcomes. To achieve these trough levels, the guidelines recommend doses of 15-20 mg/kg of actual body weight given every 8-12 hours for most patients with normal renal function, assuming a minimum inhibitory concentration (MIC) of $\leq$1 mg/L. In seriously ill patients, the guidelines recommend using a loading dose of 25-30 mg/kg to facilitate rapid attainment of the target trough serum vancomycin level. (If the MIC is $\geq$2 mg/L, then the targeted pharmacodynamic parameter for vancomycin is unachievable, and an alternative therapy should be considered.)

The pharmacodynamic parameter that best predicts efficacy for β-lactams like piperacillin is the duration of time that free drug concentrations remain above the MIC (fT>MIC), with near maximal bactericidal effects for penicillins when the free drug concentrations remain above the MIC for 50% of the dosing interval.[92] The target pharmacodynamic parameter for piperacillin-tazobactam (50% fT>MIC) may be better achieved with use of prolonged or extended infusion regimens than with intermittent, more rapidly infused, administration schedules. Lodise and coworkers recently reported that extended infusion (3.375 g intravenously [IV] for 4 hours every 8 hours) versus intermittent infusion of piperacillin-tazobactam (3.375 g IV for 30 minutes every 4 to 6 hours) was associated with a significantly lower 14-day mortality rate (12.2% vs 31.6%, $P = 0.04$) and median duration of hospital stay (21 vs 38 days, $P = 0.02$) in a cohort of hospitalized patients with a *P aeruginosa* infection.[93] Based on data such as these, the case patient here was initiated on vancomycin (15-20 mg/kg every 8–12 hours) and piperacillin-tazobactam (3.375 g IV for 4 hours every 8 hours).

CONCLUSIONS

Successful treatment of patients with serious, life-threatening hospital- or healthcare-associated infections depends on early adequate antimicrobial treatment. To accomplish this, empiric therapy is typically employed with a broad-spectrum regimen intended to cover likely causative pathogen(s) based on local antibiograms and risk factors for involvement of resistant microorganisms. Choice of empiric therapy should also be based on the site of infection, and make use of clinical practice guidelines, when available. Although this approach often means treatment with a regimen that is unnecessarily broad, based on subsequent culture findings, it is warranted based on the significant negative impact of initial inadequate/inappropriate empiric therapy, and the inability to remedy this negative effect by later modification of antimicrobial therapy. The possibility of de-escalating the initial broad-spectrum regimen is revisited after the results from cultures collected prior to beginning empiric therapy become available, generally 2-4 days after beginning

the process. In this manner, both the dangers of initial inadequate empiric therapy and overuse or misuse of antimicrobials are minimized. To further minimize the risk of antimicrobial resistance linked to overuse or misuse of antimicrobial agents, care should be taken to avoid treatment of colonization or culture contamination.

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