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INFECTIONS IN HOSPITALIZED PATIENTS:

URGENT CHALLENGES, EVOLVING MANAGEMENT

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Infections in hospitalized patients: What is happening and who can help?

ABSTRACT

The continuing emergence of multidrug-resistant bacteria calls for new approaches to the management and treatment of infections in hospitalized patients. Health care–associated infections cause substantial morbidity and mortality while driving up health care resource use and costs worldwide. The continued spread of antimicrobial resistance requires a multidisciplinary approach and closer collaboration among health care providers, especially hospitalists, pharmacists, infection control practitioners, and infectious disease specialists. Such collaboration can potentially reduce treatment failures and minimize the spread of multidrug-resistant organisms between health care settings and the community.

KEY POINTS

Surveillance studies show that antimicrobial resistance among some community-associated pathogens and several key nosocomial pathogens is increasing at an alarming rate.

Widespread emergence of resistant pathogens and transmission of some pathogens between health care and community settings suggest that providers can no longer practice in an independent or isolated manner.

Greater partnership among providers in multiple disciplines and all health care settings is urgently needed to combat the challenge of multidrug-resistant bacteria.

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Nosocomial infections, also known as hospital-acquired or health care–associated infections, are a significant public health concern. These infections are estimated to occur in 5% to 10% of acute care hospitalizations in the United States, representing more than 2 million episodes per year.[1] The highest rates are seen in intensive care units and acute care surgical and orthopedic wards. Nosocomial infections are responsible for more than 90,000 US deaths per year and millions of additional days of hospitalization; the annual cost of treating these infections in the United States is estimated to exceed $4.5 billion.[1]

Despite these substantial effects in terms of morbidity, mortality, and health care costs, many nosocomial infections can be prevented if health care providers take proper precautions when caring for patients. Providers in a wide range of disciplines—intensivists, hospitalists, surgeons, infectious disease specialists, primary care clinicians, microbiologists, nurses, pharmacists—need to collaborate and arrive at a coherent control strategy to both minimize and effectively treat these infections.

This article sets the stage for the remainder of this supplement by outlining the challenges posed by antimicrobial resistance among key nosocomial and community-associated pathogens and the rationale for multidisciplinary collaboration in combatting these challenges.

THE HEART OF THE CHALLENGES: ANTIMICROBIAL RESISTANCE

Nosocomial infections have become more troublesome in the 21st century with the spread of antimicrobial resistance. Approximately 70% of nosocomial infections are attributable to antibiotic-resistant organisms,[2] including multidrug-resistant bacterial strains, which complicates the management of infections in all health care settings (hospital, office or clinic, and nursing home).[3–6] In an increasingly complex patient population, misuse and overuse of broad-

spectrum antibiotics, coupled with suboptimal infection control practice among health care providers and institutions, have contributed to the changing scope of nosocomial infections and created new treatment challenges.

Lower respiratory tract infections (eg, ventilator-associated pneumonia), postoperative wound infections, complicated intra-abdominal infections, catheter-associated bacteremia, and urinary tract infections are the most common nosocomial infections. Bacteria are responsible for the majority of these infections, with staphylococci, enterococci, Enterobacteriaceae, and *Pseudomonas* species recovered most often. Recent surveillance studies have demonstrated that antimicrobial resistance among key nosocomial pathogens is increasing at an alarming rate.[3–6] Over the past decade, several gram-positive and gram-negative organisms have become especially problematic[5]:

- Methicillin-resistant *Staphylococcus aureus* (MRSA)
- Vancomycin-resistant enterococci
- Beta-lactam–resistant and multidrug-resistant pneumococci
- *Klebsiella pneumoniae*, *Escherichia coli*, and *Proteus mirabilis* organisms with extended-spectrum beta-lactamases (ESBLs)
- *Enterobacter* species and *Citrobacter freundii* with high-level third-generation cephalosporin (Amp C) beta-lactamase resistance
- *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Stenotrophomonas maltophilia* organisms with genes for multidrug resistance (to imipenem, fluoroquinolones, and third-generation cephalosporins).

Shifting epidemiology of methicillin-resistant *S aureus*

One particular concern is the changing epidemiology of MRSA with the appearance of these typically nosocomial strains in the community setting (ie, community-acquired MRSA).[7] Notably, the incidence of community-acquired MRSA appears to be increasing with its emergence independent of a hospital reservoir.[8–10] Community-acquired MRSA, which typically occurs in healthy, immunocompetent individuals, has been associated with serious and sometimes fatal illness (eg, necrotizing pneumonia or fasciitis),[11] likely because of its greater number of virulence factors compared with hospital-acquired MRSA strains.[7,10] Even more disturbing, however, are recent reports of transmission of community-acquired MRSA strains back into the hospital environment as a cause of nosocomial infection.[12–14] In some cases, community-acquired MRSA has replaced hospital-acquired strains, thereby creating potential infection control challenges and future antimicrobial resistance issues (ie, emerging resistance to non–beta-lactam antibiotics).

Overall, the epidemiology, infection types, and antimicrobials of choice differ between community- and hospital-acquired MRSA infections.[15,16] To best manage their patients, clinicians need to be familiar with the unique properties of these infections.

Proliferation of problematic CTX-M enzymes

Another ominous concern from the past decade is the discovery of CTX-M enzymes (named for their predominant activity against cefotaxime), which have become the most prevalent ESBLs in health care and community settings alike.[17–20] Gram-negative organisms possessing these plasmids carry aminoglycoside, tetracycline, sulfonamide, or fluoroquinolone resistance genes. While nosocomially acquired CTX-M–producing *Enterobacter* or *Klebsiella* species were initially dominant, these resistant enzymes have migrated to many other Enterobacteriaceae organisms and to *P aeruginosa*. Furthermore, ESBLs of the CTX-M type also have invaded the community setting. CTX-M–producing *E coli* is a rapidly developing problem, especially among compromised patients with community-acquired urinary tract infections (eg, those with underlying disease, recent antibiotic use, or health care contact). Although the precise mode by which these organisms are spread remains unclear, they are being isolated more frequently and are no longer confined to hospitals.[19]

Other worrisome pathogens

Other emerging pathogens of concern include carbapenem-resistant *K pneumoniae* isolates[21] and a new, highly virulent strain of *Clostridium difficile*.[22] In addition to nosocomial infections, there has been a rise in the number of community-acquired cases of *C difficile*–associated diarrhea.[22] Because both *K pneumoniae* and *C difficile* are resistant to virtually all commonly used antibiotics, control of their spread—via active surveillance, antibiotic stewardship, and meticulous attention to contact precautions—is crucial.

MULTIDISCIPLINARY COLLABORATION NEEDED

The continued emergence of multidrug-resistant gram-positive and gram-negative bacteria in health care and community settings calls for a collaborative effort to reduce treatment failures and to minimize the spread of these bacteria between health care settings and within the community. All clinicians need to keep up-to-date on resistance patterns (with the

aid of laboratory surveillance) and to administer empiric regimens that address resistance phenotypes. Overall, antimicrobial therapy choices should be effective against any likely resistant bacteria, and the optimal antimicrobial regimen is one that has a low potential to induce resistance. As antimicrobial research and development languish,[23] rational policies for prescribing existing anti-infective agents and strict infection control measures are the current mainstay efforts for preventing and curtailing multidrug-resistant bacterial infections.

Three key provider groups

The widespread emergence of resistant pathogens, including transmission of some pathogens between health care and community environments, suggests that health care providers can no longer practice in an independent or isolated manner. Traditional provider roles are well recognized, but further collaboration is needed to deal with the proliferation of multidrug-resistant organisms. Key providers who can help include primary care clinicians, hospitalists, and infectious disease specialists.

The primary care clinician is the patient's first accessible health care contact and serves as an advocate for patients as well as an intermediary between patients and the health care system.[24] The previously mentioned emergence of MRSA and *C difficile* infections in community settings demands that primary care clinicians be aware of the features of these infections and aware of appropriate treatments and infection control measures.

Hospitalists represent a relatively new physician specialty whose primary focus is the care of hospitalized patients.[25–27] Hospital medicine has been recognized as a defined field in the United States for about 10 years and is the nation's fastest-growing physician specialty. The current number of hospitalists—approximately 15,000—is anticipated to at least double in the next 5 to 10 years. As originally conceived, the role of the hospitalist is to accept "hand-offs" of hospitalized patients from primary care physicians, provide expert inpatient care to these patients, and then return these patients to the care of their primary care physicians at discharge. Hospitalists also have the opportunity to serve as systems leaders by effecting changes to improve the health outcomes of hospitalized patients. They frequently serve on hospital committees, help develop clinical guidelines, and lead multidisciplinary teams to optimize patient care.

Infectious disease specialists are often consulted in cases of undiagnosed symptoms or conditions. They diagnose and treat infections, scrutinize microbial susceptibility patterns, serve on infection control and formulary committees, establish antibiotic guidelines, provide consultation on optimal antimicrobial use in the hospital setting, and supervise parenteral antimicrobial use outside the hospital.

All of these specialties need to work together to develop a health care delivery system that will combat the urgent challenges posed by multidrug-resistant pathogens.

A need for new multidisciplinary approaches

New approaches are needed for the management and treatment of nosocomial infections caused by multidrug-resistant organisms. While several specific strategies have been suggested to improve the outcomes of patients with severe bacterial infections—such as the use of treatment guidelines, antibiotic prophylaxis restrictions, the use of antibiotics in combination, de-escalation therapy, cycling therapy,[28] and short-course therapy—a multidisciplinary approach is essential. Closer collaboration among hospitalists, pharmacists, infection control practitioners, and infectious disease specialists can potentially bridge the gap between global strategies and individual patient needs. Such collaboration also must extend to primary care clinicians and continuity-of-care providers. The need for teamwork is highlighted in recently published guidelines from the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America on developing an institutional program to enhance antimicrobial stewardship.[29]

Finally, it is impossible to overstate the importance of appropriate infection control measures and continued surveillance of resistance patterns. In many cases, surveillance efforts will require institutional support in the form of information technology services to ensure that accurate real-time information is available to clinicians and policymakers.

THE SCOPE OF THIS SUPPLEMENT

It is in this context that this journal supplement aims to update clinicians on the challenges of infections in hospitalized patients and increasing antimicrobial resistance in the 21st century. Dr. Thomas M. File, Jr, takes the supplement from here with a detailed overview of the impact of community-acquired MRSA in the hospital setting. Next, Dr. Louis B. Rice discusses emerging issues in the treatment of infections caused by multidrug-resistant gram-negative organisms. Drs. James I. Merlino and Mark A. Malangoni then describe empiric treatment options for compli-

cated skin and soft-tissue infections, and Dr. John A. Weigelt outlines empiric treatment options for complicated intra-abdominal infections. Finally, Drs. Morton P. Goldman and Radhika Nair explore the role of pharmacoeconomics in the antimicrobial formulary decision-making process as well as the economic impact of antimicrobial resistance.

Our hope is that readers will come away from this supplement better equipped to contribute to the multidisciplinary efforts urgently needed to combat the challenges posed today by serious infections. Success will demand that we all be informed and involved.

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Impact of community-acquired methicillin-resistant *Staphylococcus aureus* in the hospital setting

ABSTRACT

The epidemiology of methicillin-resistant *Staphylococcus aureus* (MRSA) is undergoing a transformation as isolates of this historically health care–associated pathogen are reported with increasing frequency in otherwise healthy community-dwelling individuals. This article provides a brief review of the differences between health care–associated and community-acquired MRSA and discusses the potential impact of the changing epidemiology of MRSA on the hospital setting.

KEY POINTS

MRSA infections are no longer limited to health care settings and appear with increasing frequency in healthy, community-dwelling individuals.

The growing presence of a community reservoir for MRSA affects control of the pathogen in the hospital setting, and gradual expansion of this reservoir can lead to failure of traditional control measures.

Strains of community-acquired MRSA have already entered the health care setting, caused nosocomial infections, and, in some cases, displaced health care–associated strains.

Reconsideration of current control strategies for MRSA in hospitals is necessary in light of the emergence of community-acquired MRSA as a clinically significant pathogen.

Dr. File reported that he received an honorarium, which he donated to a memorial fund, from Wyeth Pharmaceuticals for preparation of this article.

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Methicillin-resistant strains of *Staphylococcus aureus* (MRSA) were first described in the early 1960s, shortly after the introduction of semisynthetic penicillins. The subsequent emergence of MRSA has historically been associated with the health care setting, and this pathogen is now a common cause of nosocomial infections generally resistant to multiple antimicrobial drugs. In fact, more than half of the infections caused by *S aureus* in intensive care units and more than 40% of *S aureus* infections outside of intensive care units in US hospitals are now attributable to MRSA,[1] which causes a variety of bloodstream, respiratory/urinary tract, and skin and soft-tissue infections.

Outside of the health care setting, MRSA infections are increasingly being reported in otherwise healthy, community-dwelling individuals without health care–associated risk factors for infection.[2–5] The incidence of so-called community-associated or community-acquired MRSA (CA-MRSA) infections was first reported in the early 1980s[6,7] and has since been on the rise. Outbreaks have been reported in specific geographic locations[4,8–12] and in several well-defined and characteristically "closed" populations, including Alaskan natives, American Indians, children, participants in team sports, military personnel, and correctional facility inmates.[13–19] CA-MRSA is now the predominant cause of community-associated skin infections.[20]

DEFINING 'COMMUNITY'

A survey of the available literature reveals a lack of a standard classification system to define CA-MRSA. Related terms are often used interchangeably, and different authors use varying degrees of specificity when describing "community." This variability in nomenclature and definition has been previously noted,[4] and the need for a clearer, better-delineated classification system for MRSA infections has recently been highlighted.[21,22] The currently used system for classification of MRSA infections **(Figure 1)** will likely under-

go future revision as we gain greater insight into the changing epidemiology of this disease.

Classification guided by time of isolation, risk factors

Two primary factors currently used in the categorization of MRSA infections are *time of infection isolation* and the presence or absence of *MRSA-related risk factors* **(Figure 1)**.[4,23]

Generally, MRSA strains isolated after 48 to 72 hours of admission to a health care facility, or those present at the time of admission in recently discharged patients or residents of long-term care facilities, are interchangeably referred to as *nosocomial*, *hospital-acquired*, *hospital-associated*, or *health care–associated* MRSA (HA-MRSA).

Terms used to describe cases of infection not involving a traditional health care setting (CA-MRSA) include *community-acquired*, *community-associated*, and *community-onset*. Of these, *community-onset* is generally used to refer to infections that begin outside of the health care setting (regardless of the presence of risk factors for MRSA), while infections occurring in a community setting in the absence of risk factors for MRSA are considered by some to represent cases of "true" CA-MRSA.[24]

Characteristics of community-acquired MRSA

Current criteria set forth by the Centers for Disease Control and Prevention[25] for distinguishing CA-MRSA from HA-MRSA state that patients with CA-MRSA infection tend to have all of the following characteristics:

- Diagnosis of MRSA made in the outpatient setting or on the basis of a positive culture for MRSA within 48 hours after hospital admission
- No medical history of MRSA infection or colonization
- No history in the preceding year of hospitalization, dialysis, surgery, or admission to a nursing home, skilled nursing facility, or hospice
- No permanent indwelling catheters or medical devices that pass through the skin into the body.

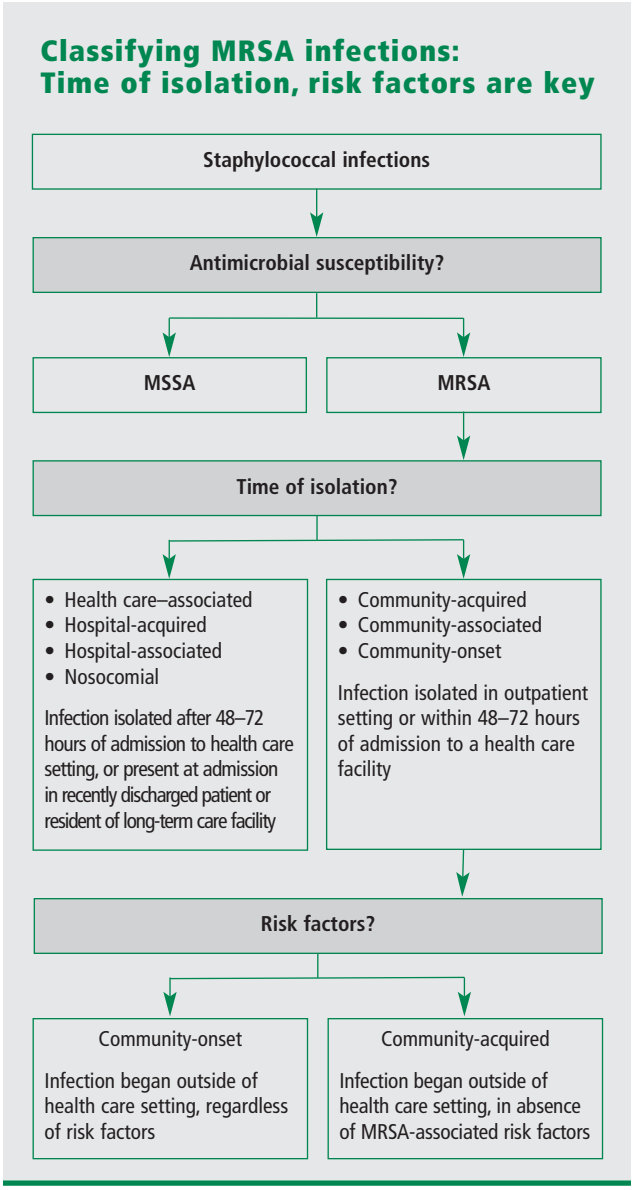

FIGURE 1. Generalized classification of infections caused by methicillin-susceptible (MSSA) and methicillin-resistant (MRSA) strains of *Staphylococcus aureus*. Based on data in references 4 and 23.

HOW COMMUNITY-ACQUIRED MRSA DIFFERS FROM HEALTH CARE–ASSOCIATED STRAINS

Community-acquired strains of MRSA are distinct from HA-MRSA strains from genotypic, phenotypic, and epidemiologic perspectives.[26–29]

At a genetic level, CA-MRSA is more similar to methicillin-susceptible *S aureus* (MSSA) than to traditional MRSA,[28] and its emergence appears to be due to the acquisition, by an MSSA strain, of the staphylococcal cassette chromosome (SCC) carrying *mec*A, the gene encoding the methicillin-resistant penicillin-binding protein.[30] Strains of CA-MRSA are more frequently susceptible to a variety of non–beta-lactam antibiotics. Although a small percentage contain SCC*mec* type V, these strains predominantly carry SCC*mec* type IV, which is smaller in size than the gene cassette found in most strains of HA-MRSA (types I, II, and III). This observed differential in SCC size may allow for more efficient transfer of resistance among different bacteria,[13] a factor that may be relevant in the alarmingly rapid emergence of CA-MRSA.

TABLE 1
Microbial profiles of health care–associated and community-acquired strains of MRSA

Strain	SCC*mec* gene	Antibiotic resistance	PFGE type	Toxins	PVL genes	Infection spectrum
HA-MRSA	Types I, II, and III	Multidrug-resistant	USA 100	Fewer	Rare	Bloodstream, respiratory tract, urinary tract infections
CA-MRSA	Types IV and V	Resistance typically limited to beta-lactams and erythromycin, although multidrug resistance can occur	USA 300	More	Common	*Commonly:* skin and soft-tissue infections *Occasionally:* necrotizing fasciitis, necrotizing pneumonia

HA-MRSA = health care–associated methicillin-resistant *Staphylococcus aureus*
CA-MRSA = community-acquired methicillin-resistant *Staphylococcus aureus*
SCC*mec* = staphylococcal cassette chromosome *mec*
PFGE = pulsed-field gel electrophoresis
PVL = Panton-Valentine leukocidin

The potential of CA-MRSA strains to cause serious illness is further underscored by their production of a relatively greater number of recognized staphylococcal virulence factors compared with HA-MRSA. Most notably, CA-MRSA strains frequently carry the Panton-Valentine leukocidin genes that produce cytotoxins associated with tissue necrosis and leukocyte destruction, although controversy remains concerning the definitive role of these genes in CA-MRSA.[31] Based on pulsed-field gel electrophoresis, almost all CA-MRSA strains are from a single clone (USA 300).[20,34]

These and other characteristics of both types of MRSA are contrasted in **Table 1**.

EMERGENCE OF COMMUNITY-ACQUIRED MRSA: EVIDENCE AND IMPLICATIONS

Reports of CA-MRSA prevalence vary widely among different studies.[4] This is due, in part, to the lack of a standard definition for CA-MRSA and differences among studies in patient setting and associated risk factors.[23,24] The overall prevalence CA-MRSA appears to be increasing.[21,24,32] In some recent studies, the percentage of community-associated *S aureus* that was resistant to methicillin has exceeded 50%.[33,34]

In one study conducted from October 2003 through February 2004 in Oakland, California, 137 emergency department patients with skin and soft-tissue infections were evaluated for CA-MRSA.[33] Of 119 infection-site cultures obtained, 79 (66.4%) grew *S aureus*, of which 61 (77.2%) were methicillin-resistant. Seventy-six percent of these cases met the clinical definition of CA-MRSA, with 99% of the MRSA strains positive for the SCC*mec* IV allele and 94% positive for Panton-Valentine leukocidin genes.

A more recent study found that MRSA was the cause of 59% of skin abscesses among adults presenting to 11 emergency departments across the United States.[20] The USA 300 strain accounted for 97% of the MRSA isolates that were typed.[20]

Community-acquired strains enter the hospital setting

Strains associated with the community setting have been introduced into hospitals in recent years, resulting in nosocomial infections and, in some cases, displacement of health care–associated strains.[5,35–39] In a 2003 meta-analysis of 27 retrospective and 5 prospective studies, CA-MRSA was found to account for 30.2% and 37.3%, respectively, of MRSA isolates from hospitalized patients.[4] While a large majority (85%) of these patients had one or more health care–associated risk factors for MRSA,[4] the remainder represent cases of "true" CA-MRSA. In this same analysis, the pooled colonization rate for MRSA among community-dwelling individuals was found to be 1.3%, with an even lower rate (0.2%) among those without *any* health care contacts. While these findings show a comparatively higher prevalence of CA-MRSA strains in the health care setting, molecular evidence shows the emergence of MRSA strains in the community to be independent of a hospital reservoir.[5,35–39]

In a more recent study that included 319 patients with CA-MRSA infection who presented to one of several rural hospitals in Idaho or Utah, 75% of these patients did not have any identified risk factor for MRSA.[40] Another study from a single medical center in Atlanta evaluated 384 persons with microbiologi-

cally confirmed community-onset *S aureus* skin infections, of which 72% were due to MRSA.[34] Among all *S aureus* isolates, 63% were considered to be community-acquired and 99% were the USA 300 clone. This rate of CA-MRSA represents a much higher percentage than reported in the meta-analysis and suggests that the actual incidence of CA-MRSA is increasing.

A threat to resistance control measures

The emergence of CA-MRSA and the growing presence of a community reservoir for methicillin-resistant strains threatens future control of antimicrobial resistance in the health care setting. Since CA-MRSA may now significantly contribute to nosocomial dissemination of MRSA within hospitals, the distinction between CA-MRSA and HA-MRSA within the hospital setting has become blurred. The migration of resistant strains from the community reservoir into hospitals is a potentially troubling development, and gradual increases in this community reservoir can be expected to lead to failure of traditional control measures. Recognition and isolation of symptomatic individuals, along with contact-tracing and quarantining, are two basic measures of control[41] that cannot be used effectively in a community setting. Isolation of infected individuals and carriers is much less manageable in a community setting compared with the relatively closed and controlled environment of the hospital. For this reason, the presence of a community reservoir from which resistant strains can recurrently be transmitted into the health care setting is a significant and growing challenge for the control of MRSA.

Differing spectrums of disease

It is important that clinicians be aware of the spectrum of disease caused by CA-MRSA, which differs from that of HA-MRSA in distribution and pattern of infection. Patients infected with CA-MRSA tend to be significantly younger than those infected with traditional strains of MRSA.[32] Unlike traditional MRSA strains, which often are isolated from the bloodstream and the respiratory and urinary tracts, CA-MRSA strains are typically found on skin and in soft tissue and occur in settings that involve crowding, contact, and compromised hygiene.[4] Interestingly, because skin infections due to CA-MRSA often have a necrotic center, many have been mistaken for spider bites.

Among 1,647 patients with CA-MRSA in a population-based surveillance study in Maryland, Georgia, and Minnesota, 77% had skin or soft-tissue infections, 10% had wound infections, 5% had respiratory tract infections (3% sinusitis, 2% pneumonia), and 4% had urinary tract infections.[42] A separate study that compared HA-MRSA and CA-MRSA infections in Minnesota found that they broke down by infection type as follows[43]:

HA-MRSA	CA-MRSA
Skin and soft tissue, 36%	Skin and soft tissue, 74%
Respiratory tract, 22%	Otitis media, 7%
Urinary tract, 20%	Respiratory tract, 6%
Bloodstream, 9%	Bloodstream, 4%
Others, 13%	Others, 9%

Stevenson et al reported similar distributions by site of infection in their study of HA-MRSA and CA-MRSA in rural communities in Idaho and Utah.[40]

Differing resistance patterns

Another difference between the two strains is that HA-MRSA is usually resistant to multiple classes of antimicrobials, whereas the usual pattern for CA-MRSA is resistance to the beta-lactams and erythromycin but susceptibility to other drugs tested. However, as CA-MRSA strains may disseminate within the hospital, it is possible that they may develop additional antimicrobial resistance. CA-MRSA strains are often susceptible to clindamycin, but the emergence of resistance during therapy has been reported, especially among erythromycin-resistant strains. Thus, an erythromycin-induction test (D-test) should be performed on such isolates to determine the presence of in vitro inducible resistance. Although these infections are generally mild in nature, more serious infections leading to hospitalization or death have occasionally been described, including bacteremia, necrotizing fasciitis, and necrotizing pneumonia.[2,10,44–48]

FUTURE NEEDS: VIGILANCE, MORE STUDIES, REVISED CONTROL MEASURES

The continuing emergence of CA-MRSA as a nosocomial pathogen is a serious public health problem that warrants increased vigilance to ensure correct diagnosis and proper management of suspected staphylococcal infections. Overall, infection with resistant strains of *S aureus* has been shown to carry a worse prognosis than infection with methicillin-sensitive strains of the pathogen, and hospitalized patients with MRSA face longer hospital stays, higher inpatient costs, and a higher mortality risk than do patients with MSSA.[49–52] This burden can only be expected to increase in the presence of a community reservoir for methicillin-resistant strains. The possibility for accumulation of added resistance patterns among CA-MRSA strains will further increase this

burden and have a significant negative impact on the hospital setting.

Our current understanding of the epidemiology of CA-MRSA is incomplete, and further studies are needed to better define optimal control measures.[53] Overall, the changing epidemiology of MRSA will require implementation of a revised set of control measures in both the hospital and community settings.

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Emerging issues in the management of infections caused by multidrug-resistant gram-negative bacteria

ABSTRACT

Accumulating evidence indicates that treating seriously ill infected patients with active antibiotics early in the course of infection is critical to improving outcomes. The most common reason for ineffective empiric therapy is resistance to the agents used. Gram-negative bacteria are becoming increasingly resistant to many commonly used antibiotics, and some cases require older, more toxic antibiotics for adequate microbial coverage. The diversity of resistance mechanisms that underly multidrug resistance makes developing effective new antimicrobial agents very difficult, especially against problematic species such as *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae*. This growing problem requires a multipronged strategy that includes adherence to infection control principles, parsimonious and rational use of current antimicrobial agents, and development of new agents active against multidrug-resistant pathogens.

KEY POINTS

Multidrug-resistant gram-negative bacteria continue to grow in importance in hospitals with high percentages of vulnerable patients. Recognizing the resistance patterns present in hospitals is key, as are empiric treatment regimens that address resistance phenotypes.

Attention to infection control measures is critical to reducing the spread of resistance, as are coherent strategies for minimizing overall antibiotic use.

Rational use of newer antibiotics that offer some activity against resistant pathogens will be important for maintaining these agents' clinical utility.

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In the past decade, patients and physicians have benefited from the introduction of several antimicrobial agents targeted toward the treatment of infections caused by drug-resistant gram-positive pathogens, primarily methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci. These agents include quinupristin-dalfopristin (Synercid), linezolid (Zyvox), daptomycin (Cubicin), and tigecycline (Tygacil) **(Table 1)**. Of these, only tigecycline has activity that extends to gram-negative pathogens,[1] although its activity is not sufficient to justify use in the treatment of infections caused by *Pseudomonas aeruginosa*.

This focus on gram-positive pathogens has been justified, given the relative dearth of agents active against these species prior to the introduction of the newer antibiotics. However, while substantial progress was made against gram-positive pathogens, a progressive increase in resistance among gram-negative pathogens has continued unabated. In many intensive care units (ICUs), multidrug-resistant gram-negative bacilli such as *P aeruginosa*, *Acinetobacter baumannii*, and *Klebsiella pneumoniae* now pose the greatest therapeutic challenge, especially for the empiric treatment of patients with systemic inflammatory response syndrome or frank sepsis.

This article will discuss the importance of effective therapy for good outcomes in critically ill infected patients, explore the mechanisms by which gram-negative bacteria have become resistant to multiple antibiotics, and review options for the treatment of multidrug-resistant gram-negative pathogens.

EMPIRIC THERAPY AND OUTCOMES: APPROPRIATE INITIAL THERAPY MATTERS

A large body of evidence has accumulated over the past decade indicating that appropriate antibacterial therapy, administered early, has a significant impact on the outcomes of serious bacterial infections **(Table 2)**.[2–7]

In an early study of ventilator-associated pneumonia from a single ICU with a small number of patients, Luna et al[2] reported substantially higher mortality

TABLE 1
Recently licensed intravenous antimicrobial agents and their activities

	Year of US approval	Extended gram-positive activity*	Broad gram-negative activity
Quinupristin-dalfopristin (Synercid)	1999	+	–
Linezolid (Zyvox)	2000	+	–
Moxifloxacin (Avelox)	2001	–	+
Ertapenem (Invanz)	2001	–	+
Daptomycin (Cubicin)	2003	+	–
Tigecycline (Tygacil)	2005	+	+

* Including methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci.

TABLE 2
Comparative mortality rates with adequate and inadequate initial antimicrobial therapy in recent studies of patients with serious bacterial infections

	Mortality rates	
Study	Adequate initial therapy	Inadequate initial therapy
Luna et al[2]	38%	91%
Rello et al[3]	15.4%	37.0%
Kollef and Ward[4]	31.3%	56.8%
Ibrahim et al[5]	28.4%	61.9%
Vallés et al[6]	37.0%	69.4%
Harbarth et al[7]	24%	39%

(91%) in patients given inadequate initial antimicrobial therapy than in those given agents active against the identified pathogen(s) (38%). The majority of inadequately treated microorganisms in this 1997 study were resistant gram-negative bacteria (*Acinetobacter* species, *K pneumoniae*, and *P aeruginosa*).

In a separate study of ventilator-associated pneumonia published that same year, Rello et al[3] found a greater than 20% increase in mortality in patients given inadequate initial antimicrobial therapy (see **Table 2** for specific rates). Most of the pneumonia cases in this study were "late" pneumonias, and *P aeruginosa* was the predominant pathogen identified.

In a 1998 study, Kollef and Ward[4] reported a mortality rate of 56.8% when a resistant pathogen was identified on mini-bronchoalveloar lavage compared with 31.3% when empiric antimicrobial regimens were active against the identified pathogen.

More recent studies have examined the impact of adequate therapy on mortality associated with bacteremia and sepsis. In a study from a university-affiliated ICU, Ibrahim et al[5] reported a mortality rate of 61.9% for inadequately treated patients with bloodstream infections compared with 28.4% for patients who received adequate therapy. *Candida* species and multidrug-resistant gram-positive bacteria predominated.

In a multicenter observational study of community-acquired bacteremia, Vallés et al[6] found that survival in the first 48 hours among patients who presented with septic shock improved by more than 25% with appropriate antimicrobial therapy **(Table 2)**. As expected with community-acquired infections, gram-positive bacteria predominated, and *Escherichia coli* represented 60% of the identified gram-negative bacteria.

Most recently, Harbarth et al[7] analyzed data gathered from a multicenter study of the safety and efficacy of the soluble tumor necrosis factor receptor fusion protein lenercept, and they found a 15% increase in mortality among patients given inadequate as opposed to adequate initial antimicrobial therapy **(Table 2)**. The most frequent bacteria for which inadequate therapy was administered in this study were *P aeruginosa*, *Stenotrophomonas maltophilia*, *Acinetobacter* species, methicillin-resistant *S aureus*, and enterococci.

It has become evident that effective therapy for ventilator-associated pneumonia and bacteremia due to a variety of microorganisms requires an initial regimen that demonstrates in vitro activity against the causative pathogen. The most common reason for inadequate therapy is resistance to the administered regimen. Therefore, understanding the mechanisms of resistance and therapy alternatives for problematic gram-negative bacteria is of profound importance.

EXPRESSION OF MULTIDRUG RESISTANCE IN GRAM-NEGATIVE BACTERIA

The expression of multidrug resistance in gram-negative bacteria hinges primarily on the presence of two characteristics:

Porins, pump mutations defend gram-negative bacteria against beta-lactams

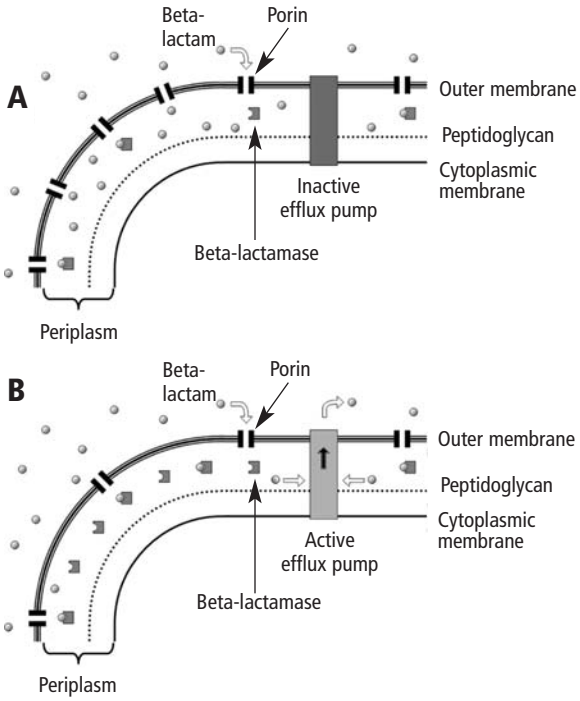

FIGURE 1. The role of porins and pump mutations in defending gram-negative bacteria against beta-lactam antibiotics. **(A)** Under circumstances in which porins are plentiful and passage through them is relatively quick, a beta-lactam has a significant advantage in that it can enter the cell in large numbers, overwhelming the number of lactamases present for defense and inhibiting enough penicillin-binding proteins to result in cell death. **(B)** After exposure to beta-lactams and other antimicrobial agents, some bacteria (notably *Pseudomonas aeruginosa*) are able to take several defensive actions. They reduce the quantity of porins in the outer membrane, retarding the beta-lactam's entry into the periplasmic space. They activate RND pumps, which "vacuum" the beta-lactams from the periplasmic space and expel them into the surrounding media. They also can increase the quantity of beta-lactamase that is produced. Under these circumstances, even a beta-lactamase that shows relatively weak activity in vitro can mount a sufficient defense to prevent cell death.

- The ability to access, then express, a variety of resistance determinants that may come from other species
- The ability to marshal intrinsic mechanisms that tend to amplify levels of resistance expressed by acquired mechanisms.

Control of periplasmic space is key

Gram-negative bacteria are structured in such a way that, to gain access to the cell, an invading compound must first traverse the outer membrane and enter the periplasmic space, a narrow region that extends from the outer membrane to the cytoplasmic membrane **(Figure 1)** and within which lies the cell wall. In the vicinity of the cytoplasmic membrane, cell wall precursors are brought out from the cytoplasm and attached to the growing and remodeling cell wall by penicillin-binding proteins, which are the targets of all beta-lactam antibiotics (penicillins, cephalosporins, carbapenems, monobactams). Thus, inhibition of penicillin-binding proteins does not require antibiotic entry into the cell itself, but simply into the periplasmic space. Controlling the periplasmic space is therefore extraordinarily important to a bacterium's survival in an antibiotic-rich environment, and this control is exerted through both nonspecific and specific mechanisms.

Nonspecific mechanisms: Porins and efflux pumps

Most solutes must enter the outer membrane of the bacterial cell by passing through protein channels known as porins.[8] All porins are not created equal, and some allow solutes to pass through more quickly than others.[8] The rate at which solutes pass through porins is referred to as the permeability of the outer membrane. Among human pathogens, *P aeruginosa* and *A baumannii* have among the most impermeable of outer membranes, giving them an immediate survival advantage in antimicrobial-rich environments. In contrast, *E coli* has a relatively porous outer membrane.[8]

Under appropriate conditions, some bacteria can reduce expression of outer membrane porins to limit entry into the periplasmic space. Perhaps the most explicit example of this is *P aeruginosa* and its expression of resistance to imipenem.[9] Of course, porins exist for purposes other than to admit antibiotics to the periplasmic space, so reductions in their content are likely to confer a selective disadvantage in an environment free of antibiotics. It is therefore not unusual for porin mutants to become less prevalent when selective pressure from antimicrobials is no longer applied.

Another mechanism for controlling the content of the periplasmic space is the expression of multidrug efflux pumps. Efflux pumps are transport proteins involved in the extrusion of toxic substrates (including antibiotics) from within cells into the external environment; multidrug efflux pumps can extrude a wide range of compounds. Research over the past decade has elucidated the impact that multidrug efflux pumps have on the expression of antibiotic resistance.

The most common and clinically important efflux pumps in gram-negative bacteria are the so-called RND (resistance–nodulation–cell division) pumps.[10] RND pumps have an outer membrane component, a cytoplasmic membrane component, and a third component that connects and holds together the other

two. Although primarily designed to extrude materials from the cytoplasm into the surrounding media, these pumps also have an opening into the periplasmic space.[11] This would theoretically allow efflux of compounds that are in the periplasmic space as well, which would explain the observation that expression of RND-type pumps has discernable impact on levels of resistance to different beta-lactam antibiotics, which do not enter the cytoplasm of bacterial cells.

Specific mechanisms: Increased beta-lactamase expression

Porin and pump mechanisms of resistance are essentially nonspecific, since porins exist to transport a variety of molecules and since pumps, while having characteristic substrate profiles, extrude a variety of compounds. In addition to these nonspecific mechanisms, gram-negative bacteria can specifically control antimicrobial action within the periplasmic space by expressing beta-lactamases. As opposed to the beta-lactamases of gram-positive bacteria (which lack outer membranes), those expressed by gram-negative bacteria are not released into the surrounding media but are largely trapped within the periplasmic space. The ability to increase expression of beta-lactamases allows gram-negative bacteria to "pack" the periplasmic space with enzymes **(Figure 1)**. Under these circumstances, even relatively weak beta-lactamases can confer a high enough level of resistance to be clinically significant.[9] When increased expression of beta-lactamase is combined with porin reductions or RND pump activations, resistance levels can be substantial.

MULTIDRUG-RESISTANT GRAM-NEGATIVE BACTERIA

Klebsiella pneumoniae

K pneumoniae differs from the other two multidrug-resistant gram-negative bacteria, *P aeruginosa* and *A baumannii*, in some important respects. Like the vast majority of gram-negative bacteria (*Salmonellae* organisms being the only known exception), *K pneumoniae* expresses a beta-lactamase that is encoded on the chromosome. Unlike the enzymes of *P aeruginosa* and *A baumannii*, however, this enzyme is constitutively (rather than inducibly) expressed and is a penicillinase with relatively weak activity against cephalosporins.[12]

Because *K pneumoniae* does not produce a cephalosporinase, it cannot easily develop resistance to cephalosporins simply by changing the regulation of its chromosomal beta-lactamase gene. Instead, *K pneumoniae* has become resistant to cephalosporins through the acquisition of cephalosporin-hydrolyzing enzymes (extended-spectrum beta-lactamases, or ESBLs).[13] In most cases, such an expansion of the substrate spectrum can be accomplished by one or two point mutations in narrow-spectrum beta-lactamase genes. These mutant genes are frequently encoded on transferable plasmids that also encode resistance to a variety of other antimicrobial agents, including trimethoprim-sulfamethoxazole, tetracyclines, aminoglycosides, and, more recently, fluoroquinolones.[14,15]

It is not clear to what extent *K pneumoniae* uses RND-type multidrug efflux pumps to express resistance to beta-lactam antibiotics. There is at least one such pump in *K pneumoniae*, activation of which has been associated with resistance to the new glycylcycline antibiotic tigecycline.[16] It is very clear, however, that *K pneumoniae* frequently uses reductions in outer membrane porins to amplify resistance. The majority of ESBL-producing *K pneumoniae* isolates in some studies have had reductions in one or more outer membrane proteins.[17] Moreover, ESBL genes are frequently found downstream of promoters that contain mutations known to increase expression.[18] Finally, ESBL-producing *K pneumoniae* strains frequently express a number of different beta-lactamases, further amplifying the quantity of beta-lactamase in the periplasmic space.[19]

One consequence of increased beta-lactamase quantity is that beta-lactamase inhibitors, which are generally quite effective at inhibiting ESBLs, become overwhelmed. As a result, in many studies the majority of ESBL-producing *K pneumoniae* isolates are also resistant to inhibitor combinations, even though the ESBLs themselves are usually susceptible to inhibition.[20]

For many years, the most reliable agents for multidrug resistant *K pneumoniae* were the carbapenems, since they were resistant to hydrolysis by ESBL-type enzymes.[21] Recently, however, *K pneumoniae* strains resistant to imipenem have appeared in different geographic locales and have spread widely in New York City. These strains produce beta-lactamases designated *K pneumoniae* carbapenemase (KPC).[22] The strains that express them are resistant to all beta-lactam antibiotics and frequently to fluoroquinolones and aminoglycosides as well. They are currently creating major therapeutic challenges in hospitals throughout the New York City area and threaten to spread elsewhere.[22]

Pseudomonas aeruginosa

P aeruginosa has as many tools for developing resistance to antibiotics as any bacterium ever studied. As noted above, the outer membrane porins of *P aeruginosa* are "slow" porins, resulting in reduced access of antibiotics to the periplasmic space.[8] In addition, *P aeruginosa* is readily able to reduce porin quantities to restrict access.

Analysis of the *P aeruginosa* genome indicates the likely presence of 12 different RND-type efflux pumps, seven of which have been characterized, with six of those seven extruding antibiotics.[23] *P aeruginosa* also has an inducible chromosomal cephalosporinase.[9] Finally, *P aeruginosa* can acquire a variety of beta-lactamases and aminoglycoside-modifying enzymes to expand the spectrum of resistance expressed.

In most instances, it appears that *P aeruginosa* uses a variety of tools to express multidrug resistance. In 2001, Dubois et al[24] reported on an outbreak of *P aeruginosa* infections in an ICU setting in which resistance to virtually all antibiotics was expressed. The strains remained moderately susceptible to cefepime (Maxipime) and amikacin. In all, 69 patients were infected with this organism. Resistance was due to a combination of efflux pump activation, porin reduction, and beta-lactamase expression. Fortunately, patients infected with this strain responded to therapeutic doses of cefepime and amikacin.

P aeruginosa also may encode metallobeta-lactamases that hydrolyze carbapenems.[25] These enzymes have been described primarily from Japan, where the use of carbapenems is more extensive than in the United States. Metalloenzymes have a broad spectrum of activity, and strains that express them are often resistant to all other beta-lactam agents (except, in some cases, aztreonam [Azactam]).[26] Multidrug resistance in *P aeruginosa* accompanied by susceptibility to aztreonam should alert clinicians to the possibility that a metallobeta-lactamase may be present.

Acinetobacter baumannii

A baumannii is similar to *P aeruginosa* in many respects, particularly in the variety of intrinsic mechanisms it uses to confer and amplify resistance. *A baumannii* porins, like those of *P aeruginosa*, are "slow,"[27] and resistance in *A baumannii* has been tied to reductions in porin quantities.[28]

Two RND-type efflux pumps have been characterized in *A baumannii*, and their combined spectrum of activity is quite broad.[29,30] *A baumannii* encodes two different chromosomal beta-lactamases, one that is a broad-spectrum cephalosporinase and a second that can hydrolyze carbapenems.[31] Acquired beta-lactamases also may amplify resistance to carbapenems.[32]

A baumannii can cause serious infections in immunocompromised patients, and outbreaks have been reported in many geographic regions. These outbreaks are focused mainly in ICUs, with ventilator-associated pneunomia, wound infections, and bloodstream infections predominating.[33] As with *P aeruginosa*, significant outbreaks of *A baumannii* infection have occurred in ICUs in the New York City area.[34,35] The strains responsible for these outbreaks tend to be resistant to multiple agents, including carbapenems. *A baumannii* has also been an important cause of serious infections in injured US soldiers returning from the Middle East, and many of these strains have expressed multidrug resistance.[36]

THERAPEUTIC OPTIONS

Before considering therapeutics, it is worth emphasizing that assiduous attention to infection control measures is critical for reducing exposure to multidrug-resistant pathogens and aborting outbreaks. Maximum judiciousness in administering antimicrobial agents is also important, since prior exposure to antibiotics is a frequent and important risk factor for colonization and infection with multidrug-resistant bacteria. Still, patients will at times become infected with multidrug-resistant bacteria, so it is important to understand what therapeutic options are available for seriously ill patients.

Options for multidrug-resistant *K pneumoniae*

Strains of *K pneumoniae* that are not multidrug-resistant are susceptible to a wide variety of commonly used antimicrobial agents, including aminoglycosides, beta-lactam/beta-lactamase inhibitor combinations, carbapenems, cephalosporins, fluoroquinolones, monobactams, and trimethoprim-sulfamethoxazole. Since many ESBL-producing strains of *K pneumoniae* encode their ESBL enzymes on large, multidrug-resistant plasmids, options for these strains are often reduced to carbapenems. In the limited clinical studies that are available, carbapenems also appear to yield the best therapeutic outcomes and are therefore recommended for treating infections known to be caused by ESBL-producing bacteria.[21,37] In selected circumstances, when in vitro susceptibility is confirmed, beta-lactam/beta-lactamase inhibitor combinations and fluoroquinolones may be used effectively. Data on the potential efficacy of the fourth-generation cephalosporin cefepime for treating ESBL infections are conflicting, so this agent cannot be confidently recommended as routine therapy for these infections at this time.

Finding alternatives for the recently emerged KPC-producing *K pneumoniae* strains is more difficult. As shown in **Table 3**, many of these strains are resistant to multiple antibiotics.[38] At present, several hospitals are using the peptide antibiotics polymyxin B or colistin (Coly-Mycin M), also known as polymyxin E, as first-line therapy for infections caused by these

strains. Another alternative is tigecycline, the recently licensed glycylcycline that exhibits excellent activity against *K pneumoniae* strains. In clinical trials supporting its licensing, tigecycline was successful in treating 46 of 52 patients with intra-abdominal infections involving *K pneumoniae*.[39] More clinical data will be required before an assessment can be made of tigecycline's efficacy against additional multidrug-resistant strains.

Options for multidrug-resistant *P aeruginosa* and *A baumannii*

Antimicrobial therapy of infections caused by *P aeruginosa* or *A baumannii* is always a challenge, even for strains with typical susceptibility patterns. Strains that are susceptible at the start of therapy often emerge resistant before the end of therapy. The resulting fear of resistance often prompts the use of combination therapy despite a lack of data to support combination therapy as a mechanism for preventing the emergence of resistance in these species. Thus, in selecting treatments for these difficult-to-treat species, we are generally operating at the edges of commonly accepted evidence-based practices.

The circumstances are even more daunting when infection is caused by strains known to be resistant to multiple drugs. Physicians are then often left with the difficult choice between commonly used antimicrobial agents that are only marginally effective in vitro or infrequently used and toxic therapies that are effective in vitro. Unfortunately, physicians in critical care settings increasingly face circumstances in which no commonly used antimicrobial agents are active in vitro against the infecting pathogen. In such circumstances, the peptide antibiotics polymyxin B and colistin are sometimes the only viable choices. Historically, these peptide antibiotics have been associated with renal toxicity and neurotoxicity. Their use diminished with the availability of broad-spectrum beta-lactam antibiotics.

Unfortunately, clinical experience with colistin and polymyxin B is scarce. Reported use of these agents against modern multidrug-resistant pathogens is rare, retrospective, and without adequate controls, which makes assessing their true efficacy difficult. The retrospective nature of the reports also often makes it difficult to accurately assess the true importance of *P aeruginosa* or *A baumannii* as a pathogen in specific cases. Finally, the serious underlying diseases that predispose to infection with these bacteria often complicate estimation of the infection's contribution to a patient's death. Despite these limitations, it is worthwhile to review the available literature on the use of these agents for these important infections.

TABLE 3
Activity of antimicrobial agents against KPC-producing, carbapenem-resistant *K pneumoniae* from Brooklyn, NY

	Susceptibility results for 96 isolates (%)		
	Susceptible	Intermediate	Resistant
Piperacillin-tazobactam (Zosyn)	0	1	99
Cefotetan (Cefotan)	59	18	23
Ceftazidime (various)	2	0	98
Cefepime (Maxipime)	40	30	30
Gentamicin (various)	61	6	33
Amikacin (various)	45	52	3
Ciprofloxacin (various)	2	0	98
Doxycycline (various)	66	10	24
Polymyxin B (Polymyxin B)	91	0	9
Tigecycline (Tygacil)	100	0	0

KPC = *Klebsiella pneumoniae* carbapenemase
Adapted from Bratu et al.[38]

Polymyxin B. In a recent study on the clinical efficacy of polymyxin B, Sobieszczyk et al[40] retrospectively analyzed 29 courses of this therapy in 25 patients with serious respiratory infections. All patients were also treated with a second antibiotic. Sixteen of the courses were in patients infected with *A baumannii* (7 resistant to all other antibiotics), 12 were in patients infected with *P aeruginosa* (5 resistant to all other antibiotics), and 1 was in a patient with *Alcaligenes xylosoxidans*. End-of-treatment mortality, the primary outcome measure, was 21%, and the outcome was judged to be favorable at the end of 22 of the 29 courses of therapy (76%). Only one course of intravenous polymyxin B was judged to be associated with significant nephrotoxicity.

Colistin. Three recent studies, all retrospective, have looked at the efficacy of colistin in treating serious gram-negative infections.[41–43]

TABLE 4
Activity of imipenem and tigecycline against 49 multidrug-resistant *Acinetobacter baumannii* strains

	MIC (μg/mL)			Susceptibility of isolates (%)		
	Range	MIC_{50}	MIC_{90}	Susceptible	Intermediate	Resistant
Imipenem-cilastatin (Primaxin)	1–128	32	128	20	2	78
Tigecycline (Tygacil)	1–4	2	2	92	8	0

MIC = minimum inhibitory concentration
Adapted, with permission, from Pachon-Ibanez et al.[47]

Garnacho-Montero et al[41] analyzed 35 cases of ventilator-associated pneumonia caused by *A baumannii*. Twenty-one of these episodes were susceptible only to colistin and were treated with colistin; the remaining 14 cases were susceptible to and treated with imipenem-cilastatin plus a second antibiotic. Clinical cure rates were 57% in both groups, and nephrotoxicity was judged to be equivalent between the groups.

Markou et al[42] reported on 28 critically ill patients treated with colistin for sepsis, 24 of whom had 26 courses and lived 48 hours so that they were deemed evaluable. Twenty episodes were due to *P aeruginosa* and 6 to *A baumannii*. Decreased fever and improved vital signs were noted in 17 of 26 colistin-treated patients for at least 48 hours, and 7 of 11 patient with bacteremia had an initial clinical response. Serious renal impairment was judged to occur in less than 10% of treatment courses.

Kasiakou et al[43] reported on 50 patients receiving 54 courses of colistin for treatment of serious infections (predominantly pulmonary and bloodstream infections) due to *A baumannii* (27 patients), *P aeruginosa* (21 patients), and *K pneumoniae* (2 patients). Virtually all patients received one or two other antimicrobial agents concomitantly. Clinical response (cure or improvement) was observed in 36 of 54 episodes (66.7%), and renal insufficiency was observed in 8% of patients.

Bottom line on peptide antibiotics. In aggregate, these small retrospective studies suggest that polymyxin B and colistin may be effective therapies for serious gram-negative infections, but better-controlled and prospective studies clearly are needed to truly define the role of these agents. On the positive side, neither agent appears to be as toxic as was once thought.

Our knowledge of these peptide antibiotics has suffered from an important limitation to date: the lack of an appropriate understanding of the pharmacodynamic parameters that will optimize their clinical efficacy. A few recent in vitro studies have investigated the pharmacodynamics of colistin and polymyxin B against *P aeruginosa*.[44–46] In general, they have found that these agents are concentration-dependent killers and have suggested that the ratio of area under the curve to minimum inhibitory concentration (AUC:MIC) is the most important parameter. They also have revealed the emergence of resistant mutants with continued dosing, a problem that has likewise been noted with nebulized forms of polymyxin B used to treat patients with cystic fibrosis.

Tigecycline. Although not effective against *P aeruginosa*, tigecycline may be an alternative for treating serious infections due to *A baumannii*. One recent in vitro study examining multidrug-resistant isolates indicates that tigecycline retains excellent activity against *A baumannii* strains that are resistant to imipenem and multiple other beta-lactam agents, confirming previous studies **(Table 4)**.[47] There are currently no published reports on the efficacy of tigecycline in treating clinical infections due to *A baumannii*. More clinical experience is required before tigecycline can be confidently recommended for treating serious infections due to *A baumannii*.

UNCERTAIN OUTLOOK FOR NEW ANTIMICROBIALS

Unfortunately, large pharmaceutical firms' investment in antibacterial therapy has waned considerably in the past decade.[48] Moreover, among the antibacterial agents that are being developed, the majority are focused on treating infections due to gram-positive bacteria.

There are several reasons for this decline. First, most gram-negative bacteria that we encounter remain susceptible to several classes of available antibiotics. Second, antibiotics are not among the most profitable drug classes being developed, even when successful. Perhaps even more important is the reality that most of the easy targets for antibacterial

therapy have already been discovered, which considerably increases the difficulty and cost of discovering new targets. Moreover, resistant gram-negative bacteria present a particular challenge since many of their resistance mechanisms are nonspecific, generic mechanisms designed to protect the organism against a wide range of toxic substances. Whereas it is easy to envision a compound that will avoid a beta-lactamase, it is much more difficult to develop a compound that will resist efflux by one of the 12 putative efflux pumps we believe *P aeruginosa* possesses.

CONCLUSIONS AND RECOMMENDATIONS

Multidrug-resistant gram-negative bacteria are with us to stay and will continue to grow in importance in hospitals that have high proportions of vulnerable patients and use excessive quantities of antibiotics. It is unlikely that a quick fix for this problem will come from the pharmaceutical industry in the near future. We must therefore use the tools available to us to reduce the spread of resistance. Attention to infection control measures is critical. Moreover, coherent strategies for minimizing total antibiotic use will be important. In addition, rational use of newer antibiotics that do offer some activity against these resistant pathogens will be important for maintaining these agents' clinical utility into the future.

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Complicated skin and soft-tissue infections: Diagnostic approach and empiric treatment options

ABSTRACT

Skin and soft-tissue infections are common and generally are uncomplicated at the time of initial presentation. However, these infections can worsen quickly when there are delays in presentation and treatment. Upon encountering these infections, physicians must respond quickly with an appropriate therapeutic plan and be aware of trends in microbial resistance in order to optimize patient care.

KEY POINTS

The primary challenge in managing skin and soft-tissue infections is to avoid delays in diagnosis and thereby prevent uncomplicated infections from progressing.

The necessary course of action can include hospitalization, prompt initiation of antimicrobial therapy, and surgical consultation.

Many patients with skin and soft-tissue infections will require surgical intervention for successful treatment.

The recent proliferation of community-acquired methicillin-resistant *Staphylococcus aureus* strains has influenced the choice of antimicrobial therapy.

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Primary care physicians are often the first to encounter patients with skin and soft-tissue infections. Many uncomplicated superficial infections resolve spontaneously with local care. Determining an exact etiology for these simple infections is often difficult and usually not necessary. Patients with these infections typically present to the physician's office or emergency department after noticing a painful red area involving the skin that has not resolved or is worsening. The initial goal should be to assess whether the patient is more seriously ill and thus harboring a more complicated infection that requires emergent intervention. If signs and symptoms of systemic involvement are present—specifically, fever, tachycardia, or hypotension—immediate hospitalization and treatment with intravenous antibiotics is necessary.

This article discusses the importance of distinguishing between complicated and less serious infections of the skin and soft tissue and reviews the microbiology, diagnosis, and empiric treatment of these infections.

DISTINGUISHING COMPLICATED INFECTIONS

Complicated skin and soft-tissue infections have been defined by the US Food and Drug Administration (FDA) using its Center for Drug Evaluation and Research criteria.[1] Specifically, there are five generally accepted conditions that identify complicated infections:

- Involvement of deep tissues, including subcutaneous fat
- Need for significant surgical intervention
- Involvement of the perianal area
- Infection of the foot in a diabetic patient
- Presence of significant coexisting diseases, including diabetes mellitus, an immunocompromised state, and obesity.

These criteria generally include patients with surgical site infection, necrotizing soft-tissue infection, and signs of systemic toxicity.

Identifying the cause of infection or the type of injury that has led to a complicated skin or soft-tissue

infection can help in discerning the likely causative organisms and guiding treatment decisions. Although these infections can be quite varied, they share a common host response that includes signs of local inflammation (erythema, edema, warmth, and tenderness) and, for more advanced infections, signs of systemic toxicity (fatigue, malaise, fever, tachycardia, and hypotension).

Uncomplicated skin infections

Uncomplicated skin infections include impetigo, erysipelas, folliculitis, furunculosis, and, in some cases, superficial cellulitis.[2–5]

Impetigo is an infection of the epidermis that can cause blisters or bullae. Erysipelas involves the dermal layer of the skin and generally presents as a painful erythematous, slightly raised lesion. Folliculitis is a superficial infection of the hair follicle, whereas furuncles are deeper infections of a single hair follicle that frequently will drain spontaneously with local care.

More complicated skin infections

More complicated skin infections include cellulitis, lymphangitis, and carbuncles.[6]

Cellulitis is a catch-all description that can include uncomplicated infections involving only the epidermis and dermis, as well as more complicated infections extending to the subcutaneous tissues. Patients with deeper infections, such as necrotizing fasciitis, septic arthritis, and osteomyelitis, often will have overlying cellulitis. Cellulitis also can occur as a response to a variety of deep inflammatory diseases that are not infectious. Therefore, patients who present with cellulitis require immediate and thorough attention in order to determine the cause, which is crucial to determining whether hospitalization, intravenous antimicrobial therapy, or surgical intervention is required.

Lymphangitis is an infection of the subcutaneous lymphatic channels and presents with erythematous streaks that are usually tender and accompanied by lymphadenopathy.

Carbuncles, like furuncles, can occur anywhere on the hairy skin. They usually extend to involve several adjacent hair follicles, which results in a coalescent inflammatory mass with multiple areas of drainage. Carbuncles tend to develop on the back of the neck and are especially likely to occur in patients with diabetes mellitus. They are generally treated with antimicrobials and incision and drainage.

Soft-tissue infections

Perianal abscesses. Isolated perianal abscesses generally are caused by cryptoglandular disease and often can be treated by simple incision and drainage.[7] Antibiotics are not necessary unless the patient has extensive surrounding cellulitis or significant coexisting diseases such as diabetes, HIV infection, or an otherwise immunocompromised state. More extensive perianal abscesses that involve deeper tissues, that have extensive surrounding cellulitis, or that occur in diabetics or otherwise immunocompromised patients require immediate surgical consultation, surgical drainage, and antimicrobial therapy.

Diabetic foot infections generally result from trauma to an insensate foot or from secondary infection of foot ulcers.[8,9] These infections can be superficial, but many involve the deeper tissues. The astute diabetic patient is generally mindful of changes consistent with superficial infection. Deeper infections may go unnoticed, however, because of a lack of sensation in the involved extremity. Any diabetic patient presenting with a lower extremity infection needs careful evaluation to rule out involvement of the deeper tissues. The deep spaces of the feet can be involved but show only subtle external signs of infection.

Underlying osteomyelitis is common in patients with diabetic foot infections and must be ruled out with careful clinical examination and radiologic studies.[8,9] A positive "probe to bone" test is a simple and highly specific correlate of osteomyelitis underlying a diabetic foot ulcer.[10] It involves lightly palpating for the presence or absence of underlying bone using a sterile instrument. When the probe detects a "rock-hard" or "gritty" structure, the presence of bone—and, by definition, osteomyelitis—is confirmed.[10]

Necrotizing soft-tissue infections are uncommon but serious and life-threatening.[11,12] Early diagnosis and rapid surgical intervention has been shown to reduce mortality. Any suspicion of a necrotizing infection should prompt immediate initiation of broad-spectrum antibiotic therapy and surgical consultation.

Early manifestations of necrotizing soft-tissue infections include tachycardia, low-grade fever, pain that is disproportionate to physical findings, and leukocytosis. The classic presentation of skin blisters, ecchymosis, bullae, or crepitus (a crackling sensation under the skin) is very specific for a necrotizing process but is present in only 10% to 40% of patients.[12] Rapid progression of these skin changes is an important and ominous sign. The presence of gas in soft tissue on computed tomography (CT) or of fascial necrosis on magnetic resonance imaging (MRI) can be diagnostic of a necrotizing soft-tissue infection in patients presenting with more subtle physical findings.

Broad-spectrum antimicrobial therapy and prompt

surgical debridement are the mainstays of treatment for patients with necrotizing soft-tissue infections. Patients showing signs of physiologic decline should be resuscitated and managed in an intensive care environment. Amputation may be necessary in up to one third of patients with necrotizing soft-tissue infections involving the extremities. Careful wound observation and repeated surgical debridement is necessary and has been shown to reduce mortality.[13]

MICROBIOLOGY

The most common skin and soft-tissue infections encountered by primary care physicians are listed in **Table 1** along with their associated causative organisms.

Skin infections. Erysipelas generally is caused by streptococcal species, usually *Streptococcus pyogenes*. Cellulitis can be caused by numerous indigenous skin organisms, which vary depending on location. Cellulitis associated with furuncles, carbuncles, or abscesses is usually caused by *Staphylococcus aureus*. More diffuse cellulitis can be caused by either streptococci or *S aureus*. Any drainage should be cultured to identify the causative organism. Although aspiration of skin has been recommended in patients with cellulitis, it is unlikely to reveal an organism and is rarely performed in practice. Blood cultures also are frequently recommended but are positive in less than 5% of cases.[6,14]

Perianal infections often are polymicrobial and usually are caused by a mix of gram-positive and gram-negative organisms, including both aerobic and anaerobic species. These infections require broader-spectrum therapy compared with cellulitis.[2,15]

Diabetic foot infections generally have involvement by *S aureus*, but studies in patients with these infections frequently identify a variety of other organisms, particularly gram-negative species. Interestingly, despite these findings, randomized controlled trials have demonstrated that treatment aimed at gram-positive species is associated with the same clinical response as broader-spectrum therapy. This suggests that many, if not all, of the gram-negative organisms identified are colonizers rather than pathogens.

Surgical site infections are caused by a variety of organisms; the type and site of operation often dictate which organisms are suspected. Infections in patients who have had clean operations frequently are caused by gram-positive organisms; in contrast, infections from operations on the gastrointestinal or genitourinary tract may be caused by gram-positive and gram-negative organisms as either monomicrobial or mixed infections.[16] The organisms most frequently implicated in surgical site infections are gram-positive and include *S aureus*, coagulase-negative staphylococci, and enterococci. Other organisms involved include *Escherichia coli* and a variety of gram-negative enteric bacteria.

TABLE 1
Microbiology of common skin and soft-tissue infections

Type of infection	Common organisms
Folliculitis	*Staphylococcus aureus*
Furuncles and carbuncles	*S aureus*
Impetigo and erysipelas	Beta-hemolytic streptococci, *S aureus*
Lymphangitis	Group A streptococci, *S aureus*
Cellulitis	Beta-hemolytic streptococci, *S aureus, Haemophilus influenzae, Staphylococcus epidermidis*
Human bites	*S aureus, S epidermidis,* streptococci (alpha- and beta-hemolytic), *Corynebacterium* spp, *Eikenella corrodens, Bacteroides fragilis*
Domestic pet bites	*Pasteurella multocida*
Abscess from intravenous drug use	*S aureus*
Diabetic foot infections	*S aureus, S epidermidis,* gram-negative bacilli

Although they are uncommon causes of surgical site infection, *S pyogenes* and *Clostridium perfringens* can lead to infection within 48 hours of operation.[17,18] Patients with infections due to these organisms usually will have minimal signs of infection at the surgical site but will report disproportionate pain and tenderness at the surgical site and show signs of systemic toxicity. Treatment involves opening the incision and performing cultures. High-dose penicillin therapy should be instituted immediately. The drainage is usually watery and has been described as "dishwater pus." If not attended to promptly, these infections progress rapidly and frequently result in death. The associated skin findings of necrotizing soft-tissue infections, such as bullae and necrosis, develop extremely late in these infections.

Necrotizing soft-tissue infections involve a variety of aerobic, facultative, and anaerobic organisms. Initial treatment with broad-spectrum antibiotics and cultures of the involved tissue are necessary because of the difficulty of predicting which organisms may be involved in a specific infection. *S pyogenes* is isolated as the single causative organism in more than half of

TABLE 2
Conditions that predispose to weakened host defenses

Diabetes mellitus	Organ transplantation
Chronic renal failure	HIV infection
Chronic steroid use	Advanced age
Chronic immunosuppressive therapy	Malnourishment

these cases.[11] It has been estimated that 15% of patients with necrotizing soft-tissue infections will not have an identified source of infection.[11]

DIAGNOSIS

Signs, symptoms, and history-taking

The classic signs and symptoms of inflammation (erythema, edema, pain, tenderness, warmth) confirm the presence of an infection. Spreading erythema is particularly concerning. The history should elicit the following: any recent injury to the infected area, intravenous drug use, any history of bites, travel history, and exposure to freshwater or saltwater. In addition, the medical history must specifically ascertain the presence of conditions or factors that might predispose to weakened immunity, such as certain diseases and the use of certain medications, particularly steroids and other immunosuppressive drugs **(Table 2)**.

Physical exam: Look beyond the infection site

A thorough physical examination is essential. While it is tempting to focus on the area of infection, a careful broader examination may reveal the underlying cause of infection. The presence of cellulitis in the lower abdominal quadrants, the groin, or even the hips may be a sign of a more remote infection, such as an incarcerated hernia or colonic diverticulitis. The examination should describe the area involved, the presence of fluctuance or crepitus, associated findings in the skin (eg, purpura, necrosis), and whether or not there is tenderness. The presence of pain and tenderness disproportionate to the associated physical findings often signals an underlying necrotizing soft-tissue infection that requires immediate attention. Crepitus is highly suggestive of a necrotizing infection. Fluctuance (a wavelike motion of a cavity containing fluid) suggests localized purulent collection that requires drainage. The borders of the infection should be outlined with an ink pen, as such a marking can be used to monitor the spread of cellulitis or the response to treatment.

Laboratory studies

Patients with complicated infection should undergo laboratory studies.[2,9] These include a complete blood cell count with differential as well as creatinine, bicarbonate, creatine phosphokinase, and C-reactive protein levels. The white blood cell count and C-reactive protein level can be determined sequentially to follow the response to therapy. Additional laboratory studies should be performed as indicated.

Patients with systemic signs of infection should have two sets of blood cultures obtained, although these are positive only infrequently. Any purulent drainage should be sent for immediate Gram stain and definitive culture and sensitivity testing. Serum glucose should be determined and normalized in diabetics and other patients in whom hyperglycemia is suspected.

Laboratory studies have a poor predictive value for the diagnosis of necrotizing soft-tissue infections. Wong et al recently proposed an index composed of laboratory values to help discriminate between necrotizing and nonnecrotizing soft-tissue infections in patients with more subtle physical findings.[19] Using six serum parameters (white blood cell count and levels of C-reactive protein, hemoglobin, serum sodium, creatinine, and glucose), they developed a weighted score to determine the risk of having necrotizing fasciitis. Their score demonstrated a positive predictive value of 92%.[19] Others have demonstrated the importance of hyponatremia in identifying patients with complicated soft-tissue infections who may be at risk for a necrotizing infection.[20]

Diagnostic imaging: Selective use can be helpful

Diagnostic imaging can be revealing but should be used selectively. Plain radiographs are indicated in patients with diabetic foot infections to ascertain the presence of osteomyelitis.[21] Plain radiographs also are useful to determine the presence of air in the soft tissues, which suggests the need for urgent surgical debridement. While CT is helpful to identify gas and fluid collections, MRI is more specific for identifying the subtle changes associated with necrotizing soft-tissue infections.[22] MRI also is superior to CT in detecting involvement of the muscular fascia. These studies are unnecessary in patients with more superficial infections and in those for whom an operation has already been deemed necessary.

ANTIMICROBIAL TREATMENT

A general algorithm for the management of soft-tissue infections is presented in **Figure 1**. A variety of antimicrobial agents may be appropriate to treat skin

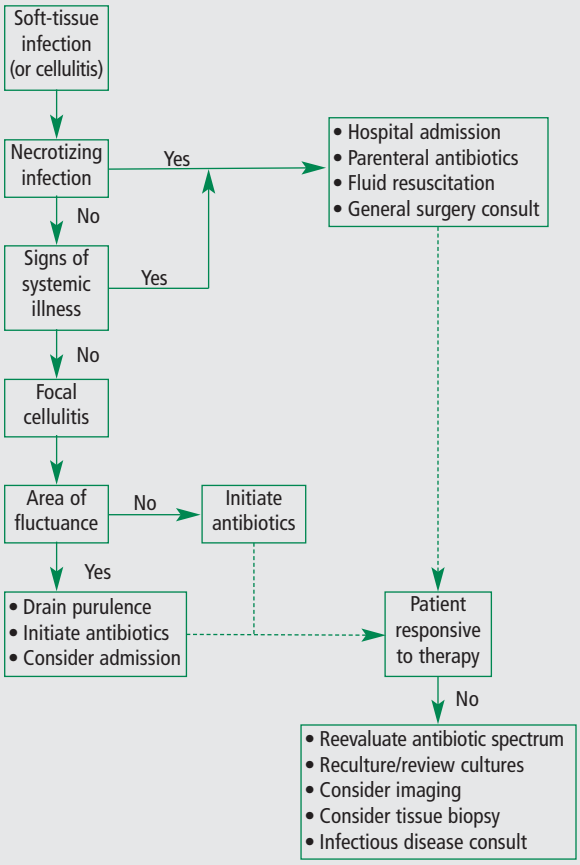

FIGURE 1. Algorithm for the management of soft-tissue infections.

and soft-tissue infections. The choice depends on the type of infection and the suspected pathogens. **Table 3** presents recommendations endorsed by the Infectious Diseases Society of America as of 2005.[2]

Penicillin is the treatment of choice for erysipelas. For cellulitis, a semisynthetic penicillin or first-generation cephalosporin should be used unless methicillin-resistant *S aureus* (MRSA) is suspected. The majority of cellulitis infections are caused by *S aureus*, but the incidence of methicillin resistance is increasing, even in community-acquired infections. In some areas of the United States, methicillin-resistant strains outnumber methicillin-sensitive strains by a 2:1 ratio.[2]

Differing approaches for community-acquired and hospital-acquired MRSA

Community-acquired MRSA can be treated with vancomycin, clindamycin, or trimethoprim-sulfamethoxazole.[23–25] Additional agents effective against community-acquired MRSA include tetracycline, linezolid (Zyvox), and gentamicin **(Table 4)**. Unfortunately, the use of gentamicin as a single agent can be associated with development of antimicrobial resistance, so gentamicin should be used only in combination.[23–25] Tigecycline (Tygacil), a new semisynthetic glycylcycline, may also represent a therapeutic option for patients hospitalized with complicated skin and skin-structure infections caused by community-acquired MRSA.[26,27]

In contrast, patients with hospital-acquired MRSA have a different antimicrobial sensitivity profile. These organisms remain sensitive to vancomycin, trimethoprim-sulfamethoxazole, tetracycline, and linezolid. Tigecycline also has been shown

TABLE 3
Recommended antimicrobial therapy for skin and soft-tissue *Staphylococcus aureus* infections in adults

Infections due to methicillin-sensitive *S aureus*	
Intravenous antibiotics	
Nafcillin (various) or oxacillin (various)	1–2 g every 4 hr
Cefazolin (various)	1 g every 8 hr
Clindamycin (various)	600 mg every 8 hr
Oral antibiotics	
Dicloxacillin (various)	500 mg 4 times daily
Cephalexin (various)	500 mg 4 times daily
Doxycycline (various) or minocycline (various)	100 mg twice daily
Trimethoprim-sulfamethoxazole (various)	1 or 2 double-strength tablets twice daily
Clindamycin	300–450 mg 3 times daily
Infections due to methicillin-resistant *S aureus*	
Intravenous antibiotics	
Vancomycin (various)	30 mg/kg/d in 2 divided doses
Linezolid (Zyvox)	600 mg every 12 hr
Clindamycin	600 mg every 8 hr
Daptomycin (Cubicin)	4 mg/kg every 24 hr
Oral antibiotics	
Linezolid	600 mg twice per day
Clindamycin	300–450 mg 3 times daily
Doxycycline or minocycline	100 mg twice daily
Trimethoprim-sulfamethoxazole	1 or 2 double-strength tablets twice daily

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TABLE 4
Pros and cons of drugs active against MRSA

Drug	Pros	Cons
Trimethoprim-sulfamethoxazole (various)	High efficacy, oral form, inexpensive	
Tetracycline (various)	High efficacy, oral form, inexpensive	Contraindicated in pregancy
Clindamycin (various)	Oral form, inexpensive	Effective vs community-acquired strains only, *Clostridium difficile*–associated colitis
Vancomycin (various)	High efficacy	IV only, ototoxicity, nephrotoxicity, expensive
Linezolid (Zyvox)	High efficacy, oral form	Myelosuppression (reversible), expensive
Daptomycin (Cubicin)	High efficacy, bactericidal	IV only
Gentamicin (various)		Moderate efficacy vs hospital-acquired strains, IV only, nephrotoxicity, ototoxicity
Tigecycline (Tygacil)	Active vs both gram-positive and gram-negative bacteria	IV only, expensive, contraindicated in pregnant women and children

MRSA = methicillin-resistant *Staphylococcus aureus*; IV = intravenous

to be effective against complicated skin and skin-structure infections caused by MRSA,[28] and the safety and efficacy of tigecycline monotherapy in these infections was recently established in two phase 3 studies.[29] Gentamicin resistance is more common, and most strains are not sensitive to clindamycin.[23–25] Most of the skin and soft-tissue infections that involve hospital-acquired MRSA do not involve other organisms.

Linezolid has been shown effective against skin and soft-tissue infections caused by MRSA. This should not be the first line of therapy, however, and should be considered only when there is culture-documented evidence of resistance or when there is nonresponse in a patient considered to be at high risk, such as with compromised immune function or prolonged exposure to an institutional environment. Daptomycin (Cubicin) has similar documented efficacy, and is bactericidal.[30,31]

TABLE 5
Recommended antimicrobial therapy for necrotizing infections in adults*

Mixed infection	
Ampicillin-sulbactam (various)	1.5–3.0 g every 6–8 hr
or	
piperacillin-tazobactam (Zosyn)	3.375 g every 6–8 hr
plus	
clindamycin (various)	600–900 mg every 8 hr
plus	
ciprofloxacin (various)	400 mg every 12 hr
Imipenem/cilastatin (Primaxin)	1 g every 6–8 hr
Meropenem (Merrem)	1 g every 8 hr
Ertapenem (Invanz)	1 g every day
Cefotaxime (various)	2 g every 6 hr
plus	
metronidazole (various)	500 mg every 6 hr
or	
clindamycin	600–900 mg every 8 hr
Streptococcal infection	
Penicillin (various)	2–4 million U every 4–6 hr
plus	
clindamycin	600–900 mg every 8 hr
***Staphylococcus aureus* infection**	
Nafcillin (various)	1–2 g every 4 hr
Oxacillin (various)	1–2 g every 4 hr
Cefazolin (various)	1 g every 8 hr
Vancomycin (various) (for resistant strains)	30 mg/kg/d in 2 divided doses
Clindamycin	600–900 mg every 8 hr
Clostridial infection	
Clindamycin	600–900 mg every 8 hr
Penicillin	2–4 million U every 4–6 hr

*All listed agents are given intravenously for these infections.

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Recommendations for specific soft-tissue infections

Perianal infections should be treated with broad-spectrum therapy if there is significant associated cellulitis. Few randomized clinical trials have assessed the treatment of these infections. The duration of therapy varies depending on the severity of infection. Patients with localized infections can be treated with incision and drainage alone. Patients with deep infections, diabetes, risk factors for compromised immune

function, or inflammatory bowel disease should be treated with a short course of therapy.

Diabetic foot infections respond well to agents that are effective against *S aureus*. The use of additional antimicrobials effective against the multitude of microorganisms that are often cultured in these patients is not associated with better outcomes than is antistaphylococcal therapy alone.[8,9]

Surgical site infections. Most patients who develop surgical site infections respond to removal of sutures and opening of the incision. Antimicrobial treatment is required if systemic signs of toxicity are present, if the associated erythema extends more than a few centimeters from the incision edge, if there is tissue necrosis, if the infection involves the muscular fascia, or if the patient has compromised immune function. The choice of antimicrobial therapy is predicated on the expected organisms, which are determined on the basis of the principles discussed above.

Necrotizing soft-tissue infections. Recommendations for the treatment of these infections are presented in **Table 5**. Some necrotizing soft-tissue infections can be associated with streptococcal toxic shock syndrome. This syndrome is caused by group A streptococci and should be treated with both clindamycin and penicillin.[2] Clindamycin has been shown to suppress toxin production and reduce cytokine production.

General treatment considerations

Many patients with complicated skin and soft-tissue infections may require surgical intervention to achieve an appropriate response. In these circumstances, antimicrobial therapy alone will not be successful.[32] Once appropriately treated, these patients should show rapid regression of infection. Patients who do not respond to initial therapy must be considered to have an undiagnosed deep infection or infection with an antimicrobial-resistant organism. In these circumstances, selection of a different agent or initiation of broader antimicrobial coverage should be considered.

Gram stain results should be checked, as they may identify unsuspected organisms. Culture and sensitivity test results also should be checked. Identification of a resistant organism should prompt a change in antibiotics. If possible, the antimicrobial spectrum should be narrowed based on the culture and sensitivity results.

SUMMARY

Skin and soft-tissue infections are common, and most are uncomplicated. The true challenge of managing these infections is to avoid delays in diagnosis and thereby prevent uncomplicated infections from progressing. The physician who encounters a skin or soft-tissue infection must respond quickly with an appropriate therapeutic plan. This can include hospitalization, prompt initiation of antimicrobial therapy, and surgical consultation. In many patients, successful treatment will require surgical intervention. The recent proliferation of community-acquired MRSA has affected the choice of antimicrobial therapy. Physicians need to be aware of these changing trends in microbial resistance to optimize care for patients with complicated skin and soft-tissue infections.

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Empiric treatment options in the management of complicated intra-abdominal infections

ABSTRACT

Complicated intra-abdominal infections remain a major challenge for surgeons and internists because of their association with high morbidity and mortality. For optimal outcome, these infections require a combination of appropriate and timely surgical source control and adjunctive broad-spectrum antimicrobial therapy. This review discusses criteria for choosing empiric antimicrobial therapy, outlines available treatment options, and highlights new antimicrobial therapies for these infections.

KEY POINTS

Source control for complicated intra-abdominal infections remains the most important component of successful treatment. Proper selection of empiric antibiotic therapy is adjunctive but important in the overall treatment approach.

Selection of empiric antimicrobial therapy for complicated intra-abdominal infections depends on the severity of illness and how the infection was acquired.

The diverse bacteriology of complicated intra-abdominal infections and the emergence of bacterial resistance make the antimicrobial treatment of these infections an important clinical challenge.

Emerging resistance of many gram-negative enteric pathogens and *Bacteroides fragilis* continues to stimulate the search for effective new antimicrobials.

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Upside Endeavors, a medical education company, prepared an initial outline and reference list for this article, which the author revised, added to, and developed into the final manuscript.

Because of their association with high rates of morbidity and mortality, intra-abdominal infections remain one of the major challenges facing surgeons and internists. Although approximately 80% of intra-abdominal infections are acquired outside of the health care setting,[1] the threat of infection with health care–associated pathogens is concerning, given the rapid colonization of hospitalized patients with resistant bacteria.

Source control (surgical measures to eradicate a focus of infection, prevent ongoing microbial contamination, and restore functional anatomy) is fundamental to the management of patients with complicated intra-abdominal infections. Empiric antimicrobial therapy, although adjunctive, is nevertheless important in the overall management plan, and the search for the optimal antimicrobial regimen continues. After beginning with an overview of intra-abdominal infections, this review focuses on criteria for choosing empiric antimicrobial therapy for complicated infections and on the available and emerging therapeutic options for these infections.

CAUSES AND CLASSIFICATION OF INTRA-ABDOMINAL INFECTIONS

More than a century ago, aerobic and anaerobic bacteria were each implicated as probable causes for the development of intra-abdominal infections. With the availability of advanced anaerobic culture techniques, it became firmly established by the mid-1970s that serious intra-abdominal infections involved synergistic mixtures of bacteria.[2]

Intra-abdominal infections generally occur because a normal anatomic barrier is disrupted. The most common disruptions occur in hollow viscera, allowing intraluminal bacteria to invade and proliferate in typically sterile regions such as the peritoneal cavity or the retroperitoneum.

Peritonitis: Wide variations in presentation

Although the term *peritonitis* is often used synonymously for intra-abdominal infections, the degree of

Peritonitis at a glance

Primary bacterial peritonitis refers to spontaneous bacterial peritonitis that arises without a breach in the peritoneal cavity. It is most commonly seen in infancy and early childhood and in patients with cirrhosis or compromised immune function.

Secondary bacterial peritonitis occurs secondary to spillage of gut organisms through a hole in the gastrointestinal tract. It may be community-acquired or health care–associated.

Tertiary peritonitis is characterized by persistent or recurrent infection that typically occurs at least 48 hours after apparently adequate management of primary or secondary peritonitis. It is most often seen in patients with significant comorbidities and in those with compromised immune function.

peritoneal involvement can vary greatly. Clinical presentation of intra-abdominal infections varies from localized appendicitis to diffuse inflammation of the abdominal cavity, characterized as generalized peritonitis. Intra-abdominal infections also can be described as primary, secondary, or tertiary peritonitis (see "Peritonitis at a glance" sidebar). Whereas primary infections usually do not involve a hollow viscus, secondary infections are associated with hollow viscus perforations. Tertiary infections are associated with immunocompromised patients and usually involve treatment failures.[3,4] Tertiary peritonitis is defined as the persistence or recurrence of intra-abdominal infection despite what appears to be have been adequate source control and appropriate antimicrobial therapy. It also may be associated with bacteria that are usually considered to have low virulence, such as enterococci and *Staphylococcus epidermidis*.[5]

Uncomplicated vs complicated infections

Intra-abdominal infections also can be categorized as uncomplicated versus complicated, although the distinction is not always clear. Complicated intra-abdominal infections are often defined as extending beyond the hollow viscus of origin into the peritoneal space with associated abscess formation or peritonitis.[1] These infections are potentially serious medical conditions that require an invasive procedure for source control.[1]

DESPITE PROGRESS, STILL A MAJOR BURDEN

The overall incidence of intra-abdominal infections is difficult to establish and varies with the underlying abdominal disease processes. The clinical significance of complicated intra-abdominal infections is often measured by the substantial burden they place on health care resources in terms of the need for emergency room services, hospital admission, imaging and laboratory diagnostics, and surgery (both initial and repeat interventions).[6] In addition, ineffective initial empiric antimicrobial therapy can significantly increase the cost of treating intra-abdominal infections, underscoring the need for prompt and appropriate interventions.[6]

Tremendous progress has been made over the past century in the management of intra-abdominal infections, as mortality rates have dropped from approximately 90% in 1900 to 23% in 2002.[7] However, mortality rates still can vary widely depending on the source of the infection, ranging from 0.25% for the appendix[8] to much higher rates for the stomach/duodenum (21%), pancreas (33%), small bowel (38%), large bowel (45%), and biliary tract (50%).[9]

Although outcomes have improved, complicated intra-abdominal infections still are associated with a high rate of mortality related to organ dysfunction in critically ill surgical patients. As a result, these infections require a combination of appropriate and timely surgical source control and broad-spectrum antimicrobial therapy for optimal outcomes. The ultimate treatment goals are to avoid invasive sepsis/bacteremia, local destructive effects of infection, and death.

RISK STRATIFICATION

Many factors can contribute to the severity of an intra-abdominal infection and to a patient's risk for a poor outcome. These include patient age, underlying comorbidities (eg, diabetes, cardiovascular disease, cancer), the extent of infection, where the infection was acquired (community vs health care setting), the presence of compromised organ function or sepsis, nutritional status, and the success of initial source control procedures.[1,10]

Dividing patients with intra-abdominal infections into lower and higher risk categories is not always straightforward, but attempting to assess a patient's risk of treatment failure and/or death is essential to optimizing a treatment plan. Proper risk stratification also is important when comparing treatment regimens and when introducing new antimicrobial agents.

Several types of patients with complicated intra-

TABLE 1
Independent risk factors for death or treatment failure in patients with intra-abdominal infections[10]

Higher APACHE II score	Liver disease
Advanced age	Malignancy
Hypoalbuminemia	Renal disease
Hypocholesterolemia	Corticosteroid therapy
Malnutrition	Unsuccessful operation
Preoperative organ impairment	

APACHE II = Acute Physiology and Chronic Health Evaluation II

abdominal infections have been identified as being at higher risk for a poor outcome, including those with higher scores on the Acute Physiology and Chronic Health Evaluation (APACHE II) classification, poor nutritional status, hypoalbuminemia, significant cardiovascular disease, and unsuccessful surgical attempts to control the local infection.[11–16] Notably, many of these risk factors are not specifically related to intra-abdominal infection but more to the patient's physiologic status or underlying medical condition **(Table 1)**.[10]

Patients who acquire infection within the hospital also have a poorer prognosis. Several studies have demonstrated that the presence of resistant microorganisms is associated with higher rates of treatment failure.[17–19] Accordingly, the selection of empiric antimicrobial therapy is likely to influence, at least in part, clinical outcome. Stratifying patients according to the probability that they harbor health care–associated resistant pathogens is another approach that can be useful in selecting antimicrobial therapy.

BACTERIOLOGY

The bacteria that cause intra-abdominal infections are derived from the endogenous flora of the gastrointestinal tract. An appreciation of the normal microflora within the gastrointestinal tract is key to understanding the spectrum of intra-abdominal infections that may ensue. **Figure 1** lists bacteria commonly found in various segments of the gastrointestinal tract.[20]

Polymicrobial isolates are the hallmark

Polymicrobial isolates remain the hallmark of intra-abdominal infections.

The most commonly isolated aerobe is *Escherichia coli*, and the most commonly isolated anaerobe is *Bacteroides fragilis*.[1,4,10] Other *Bacteroides* isolates include *Bacteroides distasonis*, *Bacteroides ovatus*, *Bacteroides thetaiotaomicron*, and *Bacteroides vulgatus*.

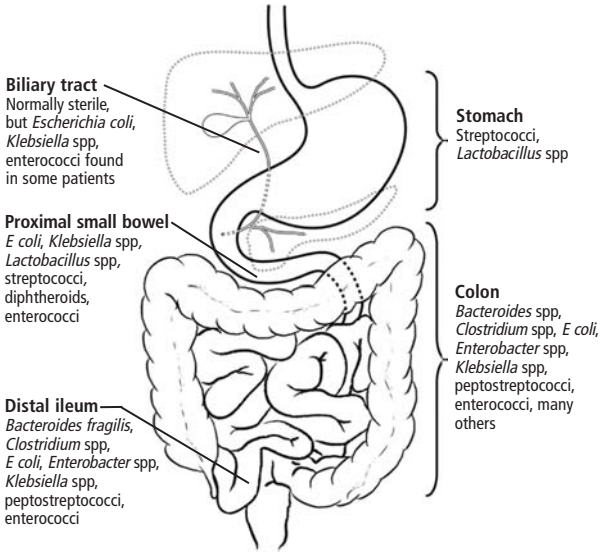

FIGURE 1. Usual microflora of the gastrointestinal tract.

The role of enterococci in intra-abdominal infections remains controversial, but treatment failure attributable to these organisms appears to be common in high-risk patients.[21–23] When enterococci are isolated, *Enterococcus faecalis* and *Enterococcus faecium* account for 90% and 10% of episodes, respectively.[24]

Pseudomonas aeruginosa and other enteric gram-negative bacteria (eg, *Acinetobacter* species) are other potential pathogens of concern because they are increasingly resistant to many antimicrobials. Infection with *P aeruginosa* is typically observed in high-risk patients such as those with late-onset nosocomial infection and those who have received previous antimicrobial therapy, undergone recurrent surgeries, or both. In constrast, patients with early-onset health care–associated or community-acquired infections have a low prevalence of *P aeruginosa*.[10]

Staphylococcus aureus is also a potential pathogen with inherent antibiotic resistance issues.[25]

Type/site of infection and acquisition mode indicate likely pathogens

The likely etiology of intra-abdominal infections can be predicted based on the type of peritonitis, the site of infection, and the mode of acquisition.[1,4,10] In general, primary (spontaneous) bacterial peritonitis is typically monomicrobial (eg, streptococci, *E coli*, staphylococci), whereas secondary and tertiary peritonitis are polymicrobial mixtures of aerobic and anaerobic bac-

TABLE 2
Pathogens associated with peritonitis

Type/site of infection	Common aerobes	Common anaerobes
Primary bacterial peritonitis		
Children (spontaneous)	*Streptococcus pneumoniae,* group A streptococci	—
Cirrhosis	*Escherichia coli, Klebsiella* spp, *S pneumoniae*	—
Peritoneal dialysis	Staphylococci, streptococci	—
Secondary bacterial peritonitis		
Gastroduodenal	Streptococci, *E coli*	—
Biliary tract	*E coli, Klebsiella* spp, enterococci	*Clostridium* spp or *Bacteroides* spp (both infrequent)
Small or large bowel	*E coli, Klebsiella* spp, *Proteus* spp	*B fragilis* and other *Bacteroides* spp, *Clostridium* spp
Appendicitis	*E coli, Pseudomonas* spp	*Bacteroides* spp
Abscesses	*E coli, Klebsiella* spp, enterococci	*B fragilis* and other *Bacteroides* spp, *Clostridium* spp, anaerobic cocci
Liver	*E coli, Klebsiella* spp, enterococci, staphylococci	*Bacteroides* spp (rare)
Spleen	Staphylococci, streptococci	—
Tertiary bacterial peritonitis		
	All of the above, but more likely to involve resistant *Pseudomonas aeruginosa*, *Enterobacter* spp, enterococci, MRSA, coagulase-negative staphylococci, and *Candida* spp	All of the above

MRSA = methicillin-resistant *Staphylococcus aureus*

teria (and occasionally fungi in cases of tertiary peritonitis). In community-acquired secondary peritonitis, gram-positive and gram-negative facultative and aerobic organisms often are implicated in infections derived from the stomach, duodenum, biliary system, and proximal small bowel.

When bacteria are present with cholecystitis, the most commonly isolated organisms are *E coli*, *Klebsiella* species, and enterococci. Infections arising from perforations in the distal small bowel are typically caused by gram-negative aerobic and facultative bacteria as well as by anaerobes. For infections beyond the proximal small bowel, a variety of anaerobes must also be considered. A wide range of bacteria also may cause colon-derived intra-abdominal infections, but facultative and obligate anaerobic organisms outnumber aerobic bacteria (eg, streptococci, enterococci, gram-negative coliforms) by a ratio of 10,000:1.[26]

In health care–associated intra-abdominal infections, which typically encompass tertiary peritonitis, nosocomial isolates particular to the site of previous surgery and to the specific hospital and unit may determine which organisms are responsible.[1] Most patients with tertiary peritonitis require treatment with multiple antimicrobials, and fungal infection, especially with *Candida* species, must always be considered. The organisms most commonly associated with primary, secondary, and tertiary peritonitis are outlined in **Table 2**.

GENERAL TREATMENT APPROACH

Fluid resuscitation, source control (ie, surgical debridement, drainage, and repair), and appropriate systemic antibacterial therapy are paramount to the successful treatment of complicated intra-abdominal infections.[1,4,10] While antimicrobial agents should not be discounted in any treatment regimen for a patient with peritonitis, source control must be considered paramount. Without source control, antibiotics will not successfully treat a patient with secondary or tertiary peritonitis.

Once the diagnosis of complicated intra-abdominal infection is suspected (ie, due to presence of a systemic and local inflammatory response), it is appropriate to plan which methods will be needed for source control and to begin antimicrobial therapy immediately. Therapy need not be delayed until an exact diagnosis is established or the results of appropriate cultures are available.[1] Withholding antimicrobials or using inadequate empiric antimicrobial therapy can result in increased failure rates and increased mortality.[27–31]

ISSUES IN ANTIMICROBIAL SELECTION AND USE

Avoid inappropriate use

Routine use of full-course antimicrobial therapy is not appropriate for all patients with intra-abdominal infections. Patients with bowel injuries due to pene-

trating, blunt, or iatrogenic trauma that are repaired within 12 hours should receive only short-course (perioperative) antimicrobial therapy, as should patients with intraoperative contamination of the operative field by enteric contents under other circumstances.[1] Likewise, patients with acute perforations of the stomach, duodenum, or proximal jejunum in the absence of antacid therapy or malignancy require only perioperative antimicrobial therapy, as do patients with acute appendicitis without evidence of gangrene, perforation, abscess, or peritonitis.[1] Appropriate perioperative antimicrobial therapy in these cases is no more than 24 hours in duration.

Factors that influence antimicrobial selection

Antimicrobial therapy poses an important clinical challenge because of the diverse bacteriology of complicated intra-abdominal infections and the emergence of bacterial resistance. In general, selection of an empiric agent or combination regimen must be directed at providing reliable activity against *E coli*, other gram-negative facultative bacteria, and *B fragilis*.[1,4,10] Consideration also must be given to whether the infection was community-acquired or health care–associated **(Table 3)**. The continuing emergence of antimicrobial resistance among some gram-negative enteric pathogens and *B fragilis* has become concerning.[32–34]

Many other factors influence the selection of an antimicrobial agent, including its potential to induce bacterial resistance, its risk of hypersensitivity, its overall tolerability, its dosing frequency, and its cost. Accordingly, the search continues for an effective antimicrobial regimen that has activity against resistant pathogens, a minimal risk of side effects, a convenient dosing schedule, and potential cost benefits.

TABLE 3
Considerations in antimicrobial selection

For patients with community-acquired secondary peritonitis
Choose agents active against enteric gram-negative aerobic and facultative bacilli and against beta-lactam–susceptible gram-positive cocci
For distal small bowel and colon-derived infections and more proximal gastrointestinal perforation with obstruction, choose agents with activity against anaerobes
Avoid agents used to treat nosocomial infection in the intensive care unit, except for high-risk patients
Inclusion of agents with enterococcal coverage provides no benefit in outcomes for patients with community-acquired infections
For high-risk patients (ie, with high APACHE II score, poor nutritional status, significant cardiovascular disease, immunosuppression, or inability to obtain adequate source control), use agents with a wider spectrum of antibacterial activity
For patients with tertiary and health care–associated peritonitis
More resistant flora are routinely encountered in this setting
Organisms are similar to those in other nosocomial infections
Treatment is based on local nosocomial flora and their resistance patterns
Agents that offer enterococcal coverage are appropriate for health care–associated infections
Consider fungal infections based on the patient's history of prior antimicrobial use and underlying risk factors

APACHE II = Acute Physiology and Chronic Health Evaluation II

Available antimicrobial options

Several intravenous antibiotics have been investigated, as monotherapy or as part of a combination regimen, for the management of patients with intra-abdominal infections. The old standard of care involved double- or triple-antimicrobial therapy (eg, aminoglycoside/beta-lactam/clindamycin) to provide coverage against an array of potential pathogens. In recent years, monotherapy with imipenem/cilastatin (Primaxin) has become the new gold standard because of its broad spectrum of activity against anticipated pathogens and its relative safety and ease of use. In addition to imipenem/cilastatin,[29,35,36] contemporary agents with documented efficacy include cefoxitin,[37,38] ampicillin/sulbactam,[39] ticarcillin clavulanate (Timentin),[40] and piperacillin/tazobactam (Zosyn).[41–44] More recently, meropenem (Merrem),[45–47] ertapenem (Invanz),[48] and tigecycline (Tygacil)[49] have been shown to be effective as monotherapy.

The use of oral antibiotics (eg, ciprofloxacin, amoxicillin/clavulanate) as step-down therapy for patients with intra-abdominal infections is a relatively recent advance that can be considered in most patients.

ANTIMICROBIAL TREATMENT GUIDELINES

Antimicrobial agents and regimens currently recommended by the Infectious Diseases Society of America, the Surgical Infection Society, the American Society for Microbiology, and the Society of Infectious Disease Pharmacists are outlined in **Table 4**.[1,10] The overall evidence suggests that no regimen has been shown to be superior to another.

Low-risk patients. The general consensus is that for low-risk patients with community-acquired intra-abdominal infections (most cases of secondary peri-

TABLE 4
Recommended empiric antimicrobial regimens for treatment of intra-abdominal infections[1,10]

Type of infection	Monotherapy regimens	Combination regimens
Low-risk, community-acquired secondary peritonitis	• Ampicillin/sulbactam (various) • Ticarcillin/clavulanate (Timentin) • Ertapenem (Invanz) • Cefotetan (Cefotan) • Cefoxitin (various)	• Cefazolin (various) or cefuroxime (various) **plus** clindamycin (various) or metronidazole (various) • Ciprofloxacin (various), levofloxacin (Levaquin), or gatifloxacin (Tequin) **plus** clindamycin or metronidazole
High-risk or health care-associated secondary peritonitis and all tertiary peritonitis*	• Imipenem/cilastatin (Primaxin) • Meropenem (Merrem) • Piperacillin/tazobactam (Zosyn)	• Aminoglycoside,† aztreonam (Azactam), ciprofloxacin, or third/fourth-generation cephalosporin‡ **plus** clindamycin or metronidazole

*Regimen may need to be modified based on need to provide coverage for methicillin-resistant *Staphylococcus aureus*, coagulase-negative staphylococci, enterococci, and *Candida* species.
†Once-daily administration recommended.
‡Cefepime (Maxipime), cefotaxime (various), ceftazidime (various), ceftizoxime (Cefizox), ceftriaxone (various)

tonitis), narrow-spectrum agents such as antianaerobic cephalosporins or ampicillin/sulbactam are preferable to more costly broad-spectrum agents as well as to those with a greater risk of toxicity. Specific enterococcal coverage, although not routinely warranted for these patients, is a benefit of penicillin derivatives.

High-risk patients. Patients who are at high risk for failure (ie, with health care–associated secondary peritonitis or any form of tertiary peritonitis) should be treated with a broad-spectrum regimen with adequate coverage against gram-negative aerobic/facultative anaerobic organisms. Addition of empiric coverage for enterococci and *Candida* species should be considered on a patient-by-patient basis. Both monotherapy (eg, imipenem/cilastatin, meropenem, piperacillin/tazobactam) and combination therapy (eg, an aminoglycoside, aztreonam, ciprofloxacin, or a third-/fourth-generation cephalosporin plus an antianaerobe) are appropriate options.

Special considerations. Special consideration is required for patients with tertiary peritonitis who are likely to be infected with difficult-to-treat organisms, such as coagulase-negative staphylococci, enterococci (including vancomycin-resistant strains), multidrug-resistant gram-negative bacilli, or yeasts. Empiric therapy in these cases must consider the patient's history of previous antimicrobial therapy and local (ie, in the hospital or unit) patterns of organisms and resistance.

NEWER THERAPEUTIC OPTIONS

Tigecycline

Subsequent to the publication of the most recent guidelines for treatment of intra-abdominal infections,[1,10] tigecycline was approved by the US Food and Drug Administration (FDA) for use in patients with complicated intra-abdominal infections. Tigecycline is a glycylcycline antibiotic with expanded broad-spectrum activity in vitro against bacteria commonly associated with intra-abdominal infections. Its overall spectrum of activity includes aerobic and facultative gram-positive and gram-negative bacteria and anaerobic bacteria.[50–53] While tigecycline exhibits greater activity against many gram-negative bacteria compared with earlier-generation tetracycline compounds, it lacks reliable activity against *P aeruginosa*.[54,55] It has a distinct mechanism of action that is not affected by resistance mechanisms that are common in response to beta-lactam, tetracycline, and aminoglycoside antibiotics.

Direct comparison with imipenem/cilastatin. Tigecycline's efficacy was compared with that of imipenem/cilastatin in 1,642 patients with complicated intra-abdominal infections in two double-blind, randomized phase 3 trials whose results were reported in a pooled analysis in 2005.[49] All patients had known or suspected complicated intra-abdominal infection and underwent appropriate source control. The most common infection diagnoses were complicated appendicitis (51%) and complicated cholecystitis (14%).

Among microbiologically evaluable patients, clinical cure rates were 86.1% (441/512) with tigecycline and 86.2% (442/513) with imipenem/cilastatin (95% CI for the difference, –4.5% to 4.4%; $P < .0001$ for noninferiority).[49] Tigecycline's efficacy was noninferior to that of imipenem/cilastatin across a variety of intra-abdominal infection diagnoses **(Figure 2)**. In both treatment groups, clinical cure rates varied by the type of infection and were lower, for instance, in patients with intra-abdominal abscess and higher in patients with compli-

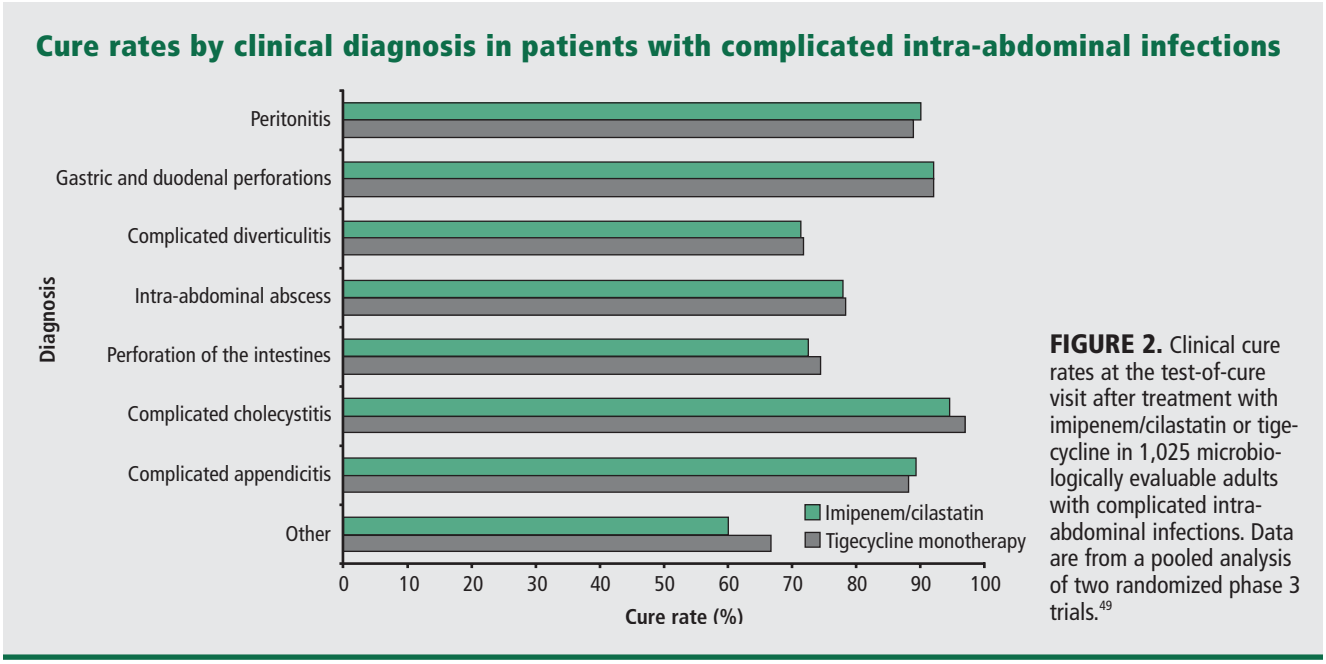

FIGURE 2. Clinical cure rates at the test-of-cure visit after treatment with imipenem/cilastatin or tigecycline in 1,025 microbiologically evaluable adults with complicated intra-abdominal infections. Data are from a pooled analysis of two randomized phase 3 trials.[49]

cated appendicitis. Not unexpectedly, patients in both treatment groups who had polymicrobial infections had a lower rate of successful outcomes compared with those who had monomicrobial infections.

Both tigecycline and imipenem/cilastatin were well tolerated in these pooled studies, with a similar frequency and distribution of treatment-emergent adverse events.[49] Gastrointestinal events were the most frequently reported adverse events in both treatment groups. Overall, the three most commonly reported adverse events were nausea (24.4% incidence with tigecycline vs 19.0% with imipenem/cilastatin; P = .010), vomiting (19.2% and 14.3%, respectively; P = .008), and diarrhea (13.8% and 13.2%, respectively; P = .719). Despite the statistically significantly higher incidence of nausea and vomiting with tigecycline, rates of premature discontinuation due to an adverse event did not differ between the two groups.

This large pooled analysis demonstrated that tigecycline was similarly efficacious and well tolerated when compared with imipenem/cilastatin in patients with complicated intra-abdominal infections.[49] No economic analysis of these agents was performed, but for a patient with normal renal function, the cost of a course of tigecycline monotherapy, based on average wholesale price,[56] is similar to that of imipenem/cilastatin for the duration of therapy used in these pooled studies (5 to 14 days). Actual drug acquisition costs and patient variables, however, would influence a formal economic evaluation.

Role in therapy. Where does tigecycline fit into clinical practice, given that many good options for treating patients with complicated intra-abdominal infections are currently available? There are a number of situations in which tigecycline might be a reasonable option, as outlined below.

- The logical patient of choice for tigecycline therapy would be one with a complicated intra-abdominal infection caused by a known resistant organism.
- Empiric therapy with tigecycline might be appropriate if local bacterial isolates from intra-abdominal infections demonstrated a resistance pattern that would make tigecycline a reasonable choice in a specific patient population based on a risk-stratification system. This would clearly be a local decision that would need to be based on objective data.
- Empiric therapy with tigecycline for a patient with tertiary peritonitis would be appropriate as long as *P aeruginosa* were not a concern. In such cases, this empiric therapy should be coupled with antifungal therapy until culture results can be obtained.

It is doubtful that tigecycline will become a first-line choice for most patients with complicated intra-abdominal infections unless an economic advantage over other regimens can be shown in future studies.

Doripenem and other investigational antimicrobials

New antibiotics for intra-abdominal infection are hard to come by these days, but a few investigational agents are on the horizon.

Doripenem is an investigational carbapenem with broad-spectrum coverage that promises to have activity against extended-spectrum beta-lactamase (ESBL)-producing gram-negative organisms.[57] A phase 3 trial comparing doripenem with an active control in patients with complicated intra-abdominal infections was recently completed[58] but has not yet been reported. A New Drug Application for doripenem was submitted to the FDA in December 2006 for indications including complicated intra-abdominal infections.

Other investigational antibiotics that do not currently appear to have a role in the therapy of abdominal infections include iclaprim, ceftobiprole, ceftaroline, and garenoxacin. As bacterial resistance rises, we can hope that the search for new antibiotics will continue.

DURATION OF ANTIMICROBIAL THERAPY

A final issue of importance to the use of antibiotics for any condition is the duration of treatment. Excessive or prolonged therapy is considered to be one driver of bacterial resistance.[59] A common problem in clinical practice is the temptation to provide extended treatment regimens to patients with intra-abdominal infection. An antimicrobial regimen for intra-abdominal infection should be continued until all presenting clinical signs and symptoms are resolved, including normalization of body temperature and white blood cell count and return to baseline gastrointestinal function.[1,4] When source control is adequate, the antimicrobial course can be restricted to 5 to 7 days.

SUMMARY AND CONCLUSIONS

Source control remains the most important component in the successful treatment of complicated intra-abdominal infections. Proper selection of empiric antibiotic therapy is adjunctive but is still important to the overall treatment plan. Selection of empiric antimicrobial therapy for complicated intra-abdominal infections depends on the severity of the illness and how the infection was acquired. Knowledge of bacterial resistance in the hospital and community must be available to inform selection of the optimal regimen. Patients with community-acquired intra-abdominal infections producing mild to moderate disease should not routinely receive extended-spectrum antibiotic regimens. Excessive use of these regimens in this population has the potential to increase bacterial resistance.[1]

A number of antibiotics have demonstrated efficacy in treating complicated intra-abdominal infections, and treatment guidelines offer specific recommendations.[1,10] However, rising rates of antibiotic-resistant bacteria in community and hospital settings highlight the need for new therapeutic options. Newer agents such as tigecycline and possibly doripenem, when available, have a potential role in the empiric treatment of complicated intra-abdominal infections when coverage is needed against gram-positive (including methicillin-resistant *S aureus* and enterococci) and gram-negative bacteria as well as aerobic and anaerobic bacteria.

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Antibacterial treatment strategies in hospitalized patients: What role for pharmacoeconomics?

ABSTRACT

Antimicrobial agents continue to account for a significant portion of institutional pharmaceutical expenditures. Pharmacoeconomic analysis is a valuable tool in assessing antibacterial agents for their place in institutional formularies. This article reviews various types of pharmacoeconomic analyses, their respective limitations, and their roles in the antibacterial formulary decision-making process. We also discuss the current state of the antibacterial pharmacoeconomic literature, including the economic impact of antimicrobial resistance.

KEY POINTS

Pharmacoeconomic analysis adds an economic component to formulary decisions while taking several factors into account, including drug acquisition costs and outcomes.

The complexity of treating infectious diseases complicates the design of robust and generalizable pharmacoeconomic studies, particularly for new antimicrobial agents.

In designing pharmacoeconomic studies, consideration should be given to study perspective, choice of analysis type and control patients, severity of illness, comorbidities, adequacy of antibacterial treatment, and ensuring clear definitions of resistance.

Antimicrobial agents remain a significant cost category in institutional pharmaceutical budgets, so their use and evaluation for formulary inclusion have important economic implications. Historically, economic evaluation of a new medication prior to formulary addition compared the new agent with existing formulary agents only in terms of acquisition cost. This is an oversimplistic approach, however, since a number of factors beyond acquisition cost may contribute to the overall cost of using one drug versus another.

This article reviews various types of pharmacoeconomic analyses that can be used to evaluate antibacterial agents and how they can contribute to antibacterial formulary decision-making. We also examine the current state of the antibacterial pharmacoeconomic literature, including the economic impact of antimicrobial resistance, as well as limitations of pharmacoeconomic analyses.

STILL A MAJOR BUDGET ITEM

In the early 1990s, antimicrobial medications accounted for as much as one third of the drug budgets of US hospitals. Although this proportion has fallen to less than one quarter in the last few years, this decline is mostly due to increases in expenditures for other drugs (eg, cardiovascular and chemotherapy agents) as opposed to representing a decline in antimicrobial expenditures.

The National Institute of Health Care Management reported that "broad-spectrum" antibacterials (eg, ciprofloxacin [Cipro and others], levofloxacin [Levaquin]) and "enhanced" antibacterials (eg, amoxicillin-clavulanate [Augmentin and others], piperacillin-tazobactam [Zosyn]) were among the 25 therapeutic categories with the highest drug expenditures from 1999 to 2001. Together these antibacterial categories accounted for 7.8% and 6.7% of total retail drug expenditures in 1999 and 2001, respectively.[1,2] The years since 2000 have seen the advent of additional new antifungal agents and new antibacterials with activity against a broad spectrum of organisms—both anaerobic and aerobic species, as well as facultative gram-positive and

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gram-negative organisms. Additionally, new agents are on the horizon to treat viral infections in hospitalized patients with compromised immune systems. Determining the appropriate use—and thus the hospital formulary status—of this multitude of antimicrobials can be complex.

FORMULARY MANAGEMENT AT A GLANCE

Formularies and formulary systems serve as an almost universal approach to rational drug utilization in US hospitals. Most institutions have a multistep approach to formulary decision-making; clear guidelines have been developed by the American Society of Health-System Pharmacists, and in-depth reviews of formulary decision-making are available.[3–7] In brief, evaluation of a new medication for the formulary typically includes a clinical, pharmacologic, safety, and toxicologic review, as well as a comparison with other medications in its class or therapeutic category and an economic evaluation.

Formulary decisions are communicated, implemented, and maintained using a number of ongoing formulary management strategies, which include drug use and clinical outcomes review, educational programs, and guidelines and restrictions for particular drugs or diseases. An institution's ability to successfully implement cost-containment strategies such as appropriate-use criteria, use restrictions, guidelines, intravenous (IV)-to-oral conversions, therapeutic substitution, and automatic stop orders is often critical in the formulary decision-making process.[8,9] Astute formulary management involves evaluating these various strategies to determine whether they provide cost savings or merely shift costs, and judiciously implementing specific strategies for specific drugs or situations to provide cost savings, better outcomes, and/or better patient care.

PHARMACOECONOMICS: RATIONALE AND APPLICATIONS

The growing demand to evaluate the actual results of health care interventions has spurred the growth of outcomes research, which evaluates the effect of interventions on patient-related (if not patient-specific) clinical outcomes, economic outcomes, and humanistic outcomes (eg, patient satisfaction and quality of life).[10]

Pharmacoeconomics is a subset of outcomes research focused on describing and analyzing the costs of drug therapy to health care systems and society.[11] It involves the comparison of costs and consequences (clinical, economic, humanistic) of interventions with pharmaceutical products and services.[12] The different costs that may be included in pharmacoeconomic analyses are outlined in the sidebar on this page. The costs and resources to be included depend on the perspective of the analysis.[10,13] For example, if the study is from a societal perspective, all types of costs should be included. However, if the study is from a hospital perspective, only direct medical costs may be included. If an intervention or program extends beyond 1 year, discounting should be applied to adjust future values to reflect the present value.[13] Although there is no set discounting rate, published standards are available (from government and previous studies).[14]

Types of costs that may be included in pharmacoeconomic analyses

Direct medical costs are the medical resources used to treat a disease or illness (eg, hospital care, drugs).

Direct nonmedical costs are the costs of nonmedical products and services that enable patients to receive treatment (eg, transportation to site of treatment).

Indirect costs are the costs of morbidity or mortality resulting from an illness (eg, loss in productivity).

Intangible costs refer to the pain and suffering caused by illness and/or treatment, and are difficult to quantify.

Beyond drug acquisition costs

Traditionally, formulary decisions took into account only drug acquisition costs, not the potential savings stemming from use of the better drug. Ideally, to merit inclusion in the formulary, a new antibacterial agent with improved efficacy should reduce the incidence and cost of treatment failure and/or result in better outcomes (or earlier achievement of comparable outcomes), which should offset the new agent's typically higher cost.[15]

Pharmacoeconomic analysis should be the preferred tool for guiding antibacterial formulary decisions and evaluating the economic impact of antibacterial use because it is usually based on clinical outcomes and does not merely evaluate drug acquisition costs. Pharmacoeconomics takes into account all types of outcomes associated with antibacterial use, such as treatment success or failure, indeterminate outcome, adverse events, and antimicrobial resistance. It also accounts for the cost of all resources used, such as professional services, hospitalization, emergency department care, laboratory tests, office visits, imaging and pathology studies, and drugs.[9]

A range of applications

Pharmacoeconomic analysis helps to identify therapies that reduce costs via efficient or optimal use of resources

Common types of pharmacoeconomic analyses

Cost-minimization analysis compares the costs of two or more interventions or treatments whose outcomes are assumed to be equivalent.[12] This type of analysis compares costs alone, whereas results in the other three types of analysis are calculated as ratios of costs to consequences. An example would be comparing the costs of using therapeutically equivalent drugs.

Cost-benefit analysis is used to compare costs and consequences of two or more alternatives with similar or different outcomes. The consequences or benefits are measured in monetary terms.[12,16] An example would be an analysis to decide whether to expand inpatient clinical services or implement an outpatient disease management program.

Cost-effectiveness analysis compares costs and consequences of alternative therapies or interventions that have similar outcomes. Unlike cost-benefit analysis, the outcomes are measured in natural units (eg, serum triglyceride levels).[12,16] A primary or intermediate outcome can be measured as the consequence of the treatment or intervention. While primary outcomes are preferred (eg, lives saved or life-years saved), intermediate outcomes may be used if the relationship between intermediate and final outcomes can be estimated.[5] An example would be comparing reductions in cardiac risk by comparing various approaches to reduce serum triglyceride levels (intermediate outcome), assuming that such a reduction would reduce cardiac risk. The cost-effectiveness ratio is presented as an average or incremental ratio. The average cost-effectiveness ratio is the ratio of the mean value of cost and outcomes (consequences) for each alternative and helps to determine the overall affordability of an intervention. The incremental cost-effectiveness ratio represents the additional cost incurred to produce the additional effect as a result of a change in therapy; it is the ratio of the change in costs and effects and provides the relative efficiency of alternative options.[5]

Cost-utility analysis, like cost-effectiveness analysis, compares the costs and consequences of alternative therapies or interventions, but is adjusted for patient preferences or utility. The effect or consequence of the therapy or intervention is measured in terms of both quality and quantity of life.[12,16] An example would be comparing chemotherapy agents for breast cancer in terms of quality-of-life–adjusted survival.

while maintaining quality patient care.[5,9] In addition, pharmacoeconomics can serve a number of specific functions that facilitate formulary decision-making in a variety of other ways; some strategies are outlined below.

- Retrospective pharmacoeconomic evaluations can help confirm the appropriateness of past formulary decisions to add or change agents.[5]
- On adding a new therapy to the formulary, an incremental analysis (to determine the additional cost incurred to provide an additional effect, measured in dollars, clinical outcomes, or utility) can be done to help assess its value relative to previous therapies.[15]
- Pharmacoeconomic analysis can help to determine if a drug is clinically or economically beneficial in different scenarios involving different populations, bacterial sensitivities, or clinical treatment strategies. It also can compare treatments using different combinations of antibacterial agents for patients with different infections and comorbid conditions.
- Pharmacoeconomic analysis can help gauge how diagnostic accuracy, monitoring (eg, adverse events), and drug-related problems may change the economic implications of a treatment. Drug-related problems such as an untreated or inappropriate indication, an improper drug or dosage, poor adherence, adverse drug reactions, or use by populations not represented in clinical trials (eg, pregnant women and children) can affect the economic efficiency of antibacterial therapy.[15] Pharmacoeconomic evaluations that account for these factors can help determine the best choice of therapy and demonstrate the economic effects of different treatment strategies in these less than ideal situations.

TYPES OF PHARMACOECONOMIC ANALYSES

Pharmacoeconomic evaluations of specific therapies may be based on one of two approaches:

- Direct observation of relevant economic outcomes (eg, costs, hospital length of stay) associated with the treatment under evaluation versus a comparator
- Modeling of expected economic outcomes based on observed clinical outcomes associated with the specific treatments and known relationships between clinical and economic outcomes from other sources.

Four types of pharmacoeconomic evaluation are typically used to assess the costs and consequences of drug therapy—cost-minimization, cost-benefit, cost-effectiveness, and cost-utility analyses. These analyses differ in the outcome measures used, as detailed in the sidebar above. Cost-effectiveness and cost-minimization analyses are the most commonly used analysis types for assessing antibacterial drugs.

All four of these types of analysis may be based on

direct observational studies, clinical trials, a modeling approach, or a combination of these, depending on the availability of economic data in the direct comparison of treatments. When modeling is used, *decision tree analysis* is the most common approach.[15] Decision tree analysis helps to identify the best decision from all available options. It involves identifying available options and predicting the consequences or outcomes of each. A likelihood or probability is assigned for each outcome, as is a cost, and the combination of all this information is used to identify the best decision option.[17]

Related analyses

Related analyses include cost-of-illness analysis and health-related quality-of-life studies.

Cost-of-illness analyses assess the resources used as a result of the illness (including treatment of the condition) and thereby determine the economic impact of the illness on society.[12] These analyses also serve to highlight the unmet therapeutic need—and corresponding economic need—for new treatments.

Health-related quality of life. In addition to the above types of pharmacoeconomic analyses, there is a growing literature on health-related quality of life. This research area provides insights into such patient outcomes as physical, social, and mental well-being and aims to provide a complete picture of the illness and its treatment.[18]

Adjust for assumptions with sensitivity analysis

Pharmacoeconomic studies conducted using any of these types of analysis will necessarily be based on a number of assumptions. For this reason it is important to conduct sensitivity analyses to determine the validity and robustness of the results obtained[5] and the limits of applying results to different patient populations and settings.[15]

PHARMACOECONOMIC ANALYSES OF ANTIBACTERIAL THERAPY: SAMPLE STUDIES

Direct comparisons of antibacterial therapies

Numerous pharmacoeconomic evaluations of antibacterial agents have been published, and a comprehensive review is beyond the scope of this article. Below we focus on a few examples of well-done pharmacoeconomic analyses with clear outcomes in order to illustrate how various types of evaluations are used. These studies were selected from the literature to represent the most common pharmacoeconomic analyses for evaluation of antibacterial drugs. Study details and major results are summarized in **Table 1**.

Cost-effectiveness analyses. Drummond et al[19] evaluated the costs, consequences, and cost-effectiveness of sequential IV and oral moxifloxacin (Avelox) monotherapy compared with amoxicillin-clavulanate with or without clarithromycin (Biaxin and others) in hospitalized patients with community-acquired pneumonia who needed parenteral treatment. Treatment with moxifloxacin resulted in more patients achieving clinical cure within 5 to 7 days after therapy, increased the speed of response, and reduced length of stay by 0.81 days **(Table 1)**. Treatment with moxifloxacin was found to be cost-effective, mainly as a result of the reduced length of stay.

Walters et al[20] attempted to determine the cost-effectiveness of three regimens—(1) sequential IV-to-oral ciprofloxacin plus IV metronidazole, (2) IV ciprofloxacin plus metronidazole, and (3) IV imipenem-cilastatin (Primaxin)—in hospitalized patients with intra-abdominal infections. Decision tree analysis was used to compare the regimens. Among patients able to receive oral therapy, sequential IV-to-oral treatment with ciprofloxacin and metronidazole was more cost-effective than the comparator regimens **(Table 1)**. Among patients unable to receive oral therapy, no differences were found among the three regimens.

Cost-minimization analyses. Samsa et al[21] compared azithromycin (Zithromax and others)–based and levofloxacin-based protocols for treating patients hospitalized with community-acquired pneumonia (see **Table 1** for specific regimens). The regimens were determined to be equally efficacious based on demonstration of clinical equivalency during the study. Data on medical resource utilization were collected through the 30 days following hospital discharge; costs of the study medications, hospital stay, home care, postdischarge medical utilization, and lost work days were included. As detailed in **Table 1**, the azithromycin-based protocol was associated with lower costs than the levofloxacin-based protocol.[21]

In a recent analysis of US patients hospitalized with complicated skin and skin structure infections, Mallick et al[22] compared hospital length of stay between those treated with IV tigecycline (Tygacil) and those treated with IV vancomycin plus IV aztreonam (Azactam). Treatment with tigecycline was associated with a shorter hospital stay after adjusting for identified risk factors **(Table 1)**. Given similar efficacy between the two treatment groups,[23] these researchers performed cost-minimization modeling to determine the economic implications of this reduction in length of stay. Based on daily costs of hospitalization for patients with complicated skin and skin structure infections identified from a US

TABLE 1
Overview of direct economic evaluations of antibacterial agents

Study (year)	Regimens compared*	Patient population	Type of analysis/ outcomes measured	Primary findings
Drummond et al[19] (2003)	• Sequential IV and oral moxifloxacin (Avelox) • Amoxicillin-clavulanate ± clarithromycin	622 hospitalized patients with CAP requiring parenteral therapy	Cost-effectiveness analysis; cost and outcomes data collected for 21 days and evaluated based on clinical cure rates 5–7 days post-treatment	• Moxifloxacin associated with higher clinical cure rate (80.7% vs 75.4%), faster response (1 day sooner for median time to first return to apyrexia), and reduced LOS (7.64 vs 8.45 days) • Moxifloxacin deemed cost-effective, yielding savings of 2,000 euros (~$2,462 in 2006 dollars) per additional patient cured, mainly due to reduced LOS
Walters et al[20] (1999)	• Sequential IV-to-oral ciprofloxacin + IV metronidazole • IV ciprofloxacin + IV metronidazole • IV imipenem-cilastatin (Primaxin)	446 hospitalized patients with intra-abdominal infections	Cost-effectiveness analysis fitted into a decision tree model to compare economic outcomes; primary clinical outcome measure was treatment success or failure as assessed by investigators	• Among patients able to receive oral therapy, sequential IV-to-oral ciprofloxacin + metronidazole was cost-effective ($7,835 per successful outcome) compared with the two IV-only treatment arms ($9,334 per successful outcome) • Among patients unable to receive oral therapy, no difference in treatment cost or success rates between IV therapies
Samsa et al[21] (2005)	• IV azithromycin + IV ceftriaxone, followed by oral azithromycin • IV levofloxacin (Levaquin) followed by oral levofloxacin	163 hospitalized patients with CAP	Cost-minimization analysis (regimens equally efficacious clinically); direct medical cost data collected through 30 days postdischarge, including study medications, hospital LOS, home care, postdischarge medical utilization, and lost work days	• Direct medical costs per patient were $2,481 lower with azithromycin-based regimen ($9,274) than with levofloxacin regimen ($11,755)
Mallick et al[22,23] (2005, 2006)	• IV tigecycline (Tygacil) • IV vancomycin + IV aztreonam (Azactam)	186 hospitalized patients with complicated skin and skin structure infections	Cost-minimization analysis (regimens equally efficacious clinically) based on pooled data on hospital LOS from two clinical trials	• Tigecycline associated with 1.85-day reduction in LOS ($P = .0015$) after adjusting for identified risk factors • Reduction in LOS translated to expected per-patient cost savings of $1,469 with tigecycline

IV = intravenous; CAP = community-acquired pneumonia; LOS = length of stay

*Except for agents with trade names listed in parentheses, the listed antibacterials are multisource drugs that are available from various manufacturers.

multihospital audit ($794),[24] modeling showed that the above reduction in length of stay with tigecyline versus vancomycin/aztreonam translated to an expected cost savings of $1,469 ($794 × 1.85 days).[23]

Discussion. All of the above four analyses were based on prospective randomized trials. Drummond et al[19] did not collect resource utilization data for the adverse events in their study, but the low incidence of adverse events suggested that such events would not have a large impact on the economic results. Walters et al[20] collected adverse event data only in terms of length of stay (ie, adverse events that extended the hospital stay). Both Drummond et al[19] and Walters et al[20] used primary outcomes (clinical cure and treatment success, respectively) as their end points.

Cost-of-illness studies

Cost-of-illness studies serve important purposes in many disease states, including complicated infections.

Such studies provide at the outset, when combined with estimates of disease prevalence, important information on the magnitude of the burden an illness poses to health care payers or to society in general. They also may serve as critical parameters for modeling the expected economic benefit of specific treatments when cost data are not directly available from head-to-head observational studies. Most cost-of-illness studies in complicated infections have focused on the public health and economic impact of antimicrobial resistance. Although this topic has been reviewed extensively,[25–27] it is helpful to consider in the present discussion.

Antimicrobial resistance. As early as 20 years ago, Holmberg et al[28] reviewed the contemporary literature and concluded that antimicrobial resistance was not only an important health problem but also an economic burden to society. Antimicrobial resistance has since been estimated to cost the United States up to $5 billion annually.[25]

However, many of the reported cost-of-illness studies have not been particularly well designed to evaluate increases in expenditures attributable to resistance. Early case-control studies did not take into account whether patient populations were infected by resistant as opposed to susceptible organisms. Some of these reports were also based on large database analyses that lacked sufficient clinical information.

Methicillin-resistant *Staphylococcus aureus* (MRSA) has been a key focus of the literature on the economic impact of resistance.[29–31] These studies have highlighted extended length of stay as the predominant driver of MRSA-related costs in patients with complicated infections.

Other studies have examined the economic impact of antimicrobial resistance in the context of other microorganisms. Three well-designed analyses are pertinent to the discussion here.[32–34]

One study was a retrospective cohort investigation that matched 233 hospitalized patients with vancomycin-resistant enterococci (VRE) (case group) on a 1:3 basis with 647 hospitalized control patients according to hospital location, date, and length of stay prior to infection.[32] The objective was to determine the economic impact of VRE. Multivariate analysis showed that VRE was associated with increases in mortality, surgical procedures, and admissions to the intensive care unit, as well as with an excess cost of more than $12,000 per case.

In a retrospective cohort study of more than 200 patients with respiratory or blood isolates of either penicillin-susceptible or -nonsusceptible *Streptococcus pneumoniae*, Klepser et al[33] found that length of stay and cost of care were significantly greater for patients in the nonsusceptible group than for those in the susceptible group. There was no difference in clinical outcomes, and patients in the nonsusceptible group had more antibiotic use prior to their present infection.

Gram-negative organisms are more complicated, since the various species likely necessitate differentiated studies. As *Pseudomonas aeruginosa* is a relatively common nosocomial isolate that poses treatment challenges, Carmeli et al[34] designed a study to evaluate the clinical and economic impact of bloodstream infections caused by resistant and susceptible *P aeruginosa,* including those organisms that became resistant during therapy. Resistance was clearly defined and outcomes included mortality, secondary bacteremia, length of stay, and hospital charges. A total of 421 patients were identified, of whom 70% had *P aeruginosa* isolates that were considered susceptible. Thirty patients had isolates that were susceptible at baseline but then became resistant during therapy. This group of patients had significant increases in mortality and length of stay relative to patients with isolates that remained susceptible throughout therapy.

Many factors affect the outcomes of patients infected with resistant organisms, including infection acuity, underlying diseases, and the actual hospital epidemiology. The definition of resistance also must be taken into consideration—ie, how many antibacterials the organism is resistant to and how effective the remaining active agents are. In addition, some organisms are more virulent than others and play a larger role in poor outcomes. It is clear, however, that resistant organisms have a significant effect on outcomes and costs. It is therefore possible that appropriate stewardship can improve antimicrobial utilization and reduce rates of resistance.[35]

Cost of inadequate initial therapy. Berger et al recently used a large US multihospital database to retrospectively examine the impact of failure of initial empiric therapy on the overall cost of hospital treatment for patients who received IV antibiotics for complicated skin and skin structure infections[24] or complicated intra-abdominal infections.[36]

Their analysis of skin and skin structure infections involved a cohort of 23,846 patients, 24% of whom experienced failure of initial IV antibiotic therapy, defined as the need for drainage/debridement or a change in antibiotic regimen (except for de-escalation or IV-to-oral switches).[24] Patients in whom initial IV antibiotic therapy failed had a threefold increase in inpatient mortality compared with those in whom ini-

TABLE 2
Clinical and economic consequences of failure of initial empiric intravenous (IV) antibiotic therapy[24,36]

Hospitalized patients with complicated skin and skin structure infections (N = 23,846)

Outcome measure	Pts with initial Tx failure	Pts with initial Tx nonfailure	*P* for difference
In-hospital mortality	1.2%	0.4%	< .001
Duration of IV antibiotic therapy (days)	8.5	4.2	< .001
Hospital length of stay (days)	9.4	5.1	< .001
Inpatient charges	$8,920	$4,142	< .001

Hospitalized patients with complicated intra-abdominal infections (N = 2,061)

Outcome measure	Pts with initial Tx failure	Pts with initial Tx nonfailure	*P* for difference
In-hospital mortality	9.3%	1.4%	< .001
Duration of IV antibiotic therapy (days)	9.9	5.1	< .001
Hospital length of stay (days)	11.3	6.7	< .001
Inpatient charges	$17,539	$9,152	< .001

tial therapy did not fail, and they received an additional 4.3 days of IV antibiotic therapy, were hospitalized an additional 4.3 days, and incurred an additional $4,778 in inpatient charges **(Table 2)**.

In the analysis of complicated intra-abdominal infections, 25% of the cohort of 2,061 patients did not respond to initial IV antibiotic therapy.[36] Compared with their counterparts who responded to initial therapy, these patients had a sixfold increase in mortality, received an additional 4.8 days of IV antibiotic therapy, stayed in the hospital 4.6 days longer, and incurred an additional $8,387 in inpatient charges **(Table 2)**.

It should be noted that these data from Berger et al are currently available only in abstract form and that both studies are retrospective reviews of a large database. It would be helpful if the definition of antibiotic failure were specified clearly, since factors such as lack of surgical intervention could influence antibiotic failure rates. On the basis of clinical experience and the information in these abstracts, it seems clear that patients who do not respond to initial interventions fare worse than those who do respond. These studies complement others[37] demonstrating that early initiation of appropriate antimicrobial therapy plays a role in clinical success.

GAPS IN THE LITERATURE

Adverse events and their treatment have an important effect on the clinical and economic benefits of antibacterial agents and should be evaluated prior to inclusion of agents in the formulary.[38] A study by Classen et al[39] showed that antibacterial-related adverse events accounted for 23.3% of all adverse drug reactions among hospitalized patients. However, very few pharmacoeconomic studies have evaluated the cost of adverse events due to antibacterial agents.[38]

An electronic literature search using MEDLINE to identify pharmacoeconomic studies of antibacterial agents retrieved a wide array of articles, with a greater number of studies on certain infections (eg, community-acquired pneumonia) than on others. Because broad-spectrum antibacterials may be used against a wide variety of infections and microorganisms, and because each organism can cause several types of infection, the number of possible organism-drug combinations is considerable. Accounting for this abundance of possible scenarios makes pharmacoeconomic evaluations and extrapolation of results complex and challenging. In addition, various infections differ in severity and may have different guidelines for treatment. Although guidelines might make it simpler to evaluate certain infections, results may not be generalizable to other infections caused by the same organism in different practice settings (eg, other hospitals or nursing homes). In addition, it may be difficult to identify clear end points or summary outcomes for treatment of certain infections.

The relevance of these types of studies plays into the design of the pharmacoeconomic evaluations described in the previous sections. The epidemiology

in an individual institution may skew the applicability of an economic analysis if resistance patterns are different from those studied, as differing prevalences of resistant organisms clearly can affect economic outcomes.

LIMITATIONS OF PHARMACOECONOMIC ANALYSES

Despite its potential utility, pharmacoeconomic analysis is associated with several general limitations as well as drawbacks specific to its use in antibacterial formulary decision-making.

Included costs are often incomplete or imprecise

A large proportion of pharmacoeconomic studies of antibacterial agents consider only the acquisition costs of the agents and do not take into account hospitalization costs, which make up a major portion of overall expenditures in the treatment of infectious diseases. Some studies take into account the acquisition and dispensing costs of the antibacterial agents and other drugs used to treat the infection and any adverse events. These studies are based on an assumption that the remainder of the costs associated with the hospitalization are fixed and constant between groups. Using hourly wages to calculate dispensing and administration costs may not have much of an impact on hospital costs. Additionally, the viability of time and motion studies to calculate labor and material costs associated with treatment may be limited. Even the inclusion of the entire cost of hospitalization may still not capture all costs related to an infectious episode because costs related to the episode may have been incurred before treatment was begun and may not be included. In addition, the infection may not be the sole reason for the hospitalization. Separating out all the costs related to other diagnoses might be difficult and thus may require the use of estimates.[40]

No single ideal method for calculating costs

The costs calculated in a prospective study may not be generalizable because most prospective studies are randomized controlled trials that do not represent normal conditions in general practice. Retrospective collection of cost data may pose difficulties in separating the costs of treating the infection from the costs of treating other diagnoses. In addition, cost data may be collected from a single institution, which limits their generalizability. Another method used to determine costs, expert opinion, is limited in that it does not report actual patient-incurred costs and does not allow for much variation, which may pose statistical challenges. As a result, no single method for calculating costs is appropriate in all situations.[40]

Each type of analysis has drawbacks

Each type of analysis has its limitations. In cost-minimization analysis, it might be difficult to establish that clinical outcomes are equivalent.[16] Cost-effectiveness analysis compares only one outcome or a single summary measure of related outcomes at a time, and some diseases may not have a distinct measure or a summary measure that can serve as an overall indicator of the effect of an intervention. In addition, cost-effectiveness analysis measures only the affordability and efficiency of a treatment and not whether the clinical outcomes gained are worth the cost of treatment.[5] The drawback of cost-benefit analysis is the difficulty of assigning monetary values to certain outcomes. For example, if the outcome or consequence evaluated is years of life saved, assigning a monetary value to life might be problematic.[12,16] Use of average ratios calculated to interpret comparisons of interventions may not reveal the magnitude of the cost and consequences or the differences between treatments. As a result, ratios do not provide useful information in terms of budget impact.[5]

Timeliness, generalizability, other limits

The timeliness of pharmacoeconomic analyses is often problematic due to the time lag associated with publication. Pharmacoeconomic studies are rarely available when formulary decisions on new drugs are being made, and even if studies are available, their reliability and robustness might be questionable. Modeling a study from different perspectives and using different assumptions may present different and sometimes contradictory results. In addition, these assumptions may be incorrect or inappropriate.[5] Moreover, pharmacoeconomic evaluations in a specific institution, under specific conditions and for specific populations, may not be applicable to other institutions or situations. Likewise, infections or illnesses may differ in degree of severity and risk, which again limits generalizability.[3] Similarly, patterns of antimicrobial resistance may develop differently over time in different settings, which further limits applicability between settings.[15] Other potential limitations include biased industry sponsorship and lack of in-house expertise in economic evaluation.[5]

CONCLUSIONS

The complexity of both infectious diseases and their treatments makes it difficult to design robust and generalizable pharmacoeconomic studies, especially for new antibacterial agents. As a result, pharmacy and therapeutics committees often must rely on studies conducted on a small scale after a drug has been intro-

duced to the market. Economic evaluation of antibacterials is important but should not be the primary driver of utilization. Careful consideration of a drug's effectiveness and safety relative to other agents on the formulary must precede economic considerations.

Translating the pharmacoeconomic literature to the individual institutional level is challenging, especially when it comes to length of stay and institution-specific resource use. Also, the issues of antimicrobial resistance and initial therapy failure should be taken into consideration so as to maximize use of the most effective agents up front and assure adequate dosing.

Despite its limitations, pharmacoeconomic analysis is a valuable tool in assessing antibacterial agents for their place in the formulary. It adds an economic component to formulary decisions while accounting for factors in addition to drug acquisition cost. When possible, institution-specific pharmacoeconomic studies should be considered to validate published data. The design of such studies should give careful consideration to the study perspective, the choice of analysis type and control patients, the severity of illness, patient comorbidities, the adequacy of antibacterial treatment, and ensuring clear definitions of resistance.

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