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InetCE

Volume 9	2005	Number 4
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Antimicrobial Resistance in Gram-Positive and Gram-Negative Bacteria

***InetCE* 221-999-05-009-H01**

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LEARNING OBJECTIVES

1. Review the epidemiology of gram-positive and gram-negative antimicrobial resistance.
2. Identify mechanisms of antimicrobial resistance in bacteria.
3. Describe appropriate steps to slow/prevent the development of resistance.
4. Review the epidemiology and management of resistant *Streptococcus pneumoniae*, methicillin-resistant *Staphylococcus aureus,* vancomycin-resistant *Enterococcus*, *Pseudomonas aeruginosa*, and *Acinetobacter* species, and extended-spectrum β-lactamase–producing enterobacteriaciae.
5. Recommend antimicrobial therapy for resistant pathogens.

ABSTRACT: Infection attributable to a resistant gram-positive or gram-negative organism has been associated with increased morbidity and mortality. Current National Nosocomial Infections Surveillance System (NNIS) data indicate increasing resistance among many hospital pathogens isolated from the intensive care units (ICUs). This review will discuss the epidemiology of the increasing resistance problem, common mechanisms of antibiotic resistance, methods to slow the development of resistance, resistance issues with specific gram-positive and gram-negative organisms, and management strategies when infection with resistant bacteria is suspected or confirmed.

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Introduction

Infection with resistant gram-positive or gram-negative organisms is associated with increased morbidity, mortality, and hospital costs.[1] Increasing resistance

rates make initiation of appropriate antimicrobials challenging for clinicians. The Centers for Disease Control and Prevention (CDC) sponsors the National Nosocomial Infection Surveillance System[2] (NNIS) that collects data on resistance rates related to several key pathogens in intensive care units (ICUs) in the United States. The most recent NNIS report (Figure 1) that compares 2003 data with the previous 5-year period (1998 to 2002) was published in October 2004. The report showed that approximately 60% of all *Staphylococcus* (*S.*) *aureus* isolates tested were resistant to methicillin. Methicillin-resistant *S. aureus* (MRSA) has been steadily increasing making empiric therapy for gram-positives with vancomycin increasingly more common. Based on the NNIS, vancomycin resistance in *Enterococcus* (*E.*) *faecium* also appears to be steadily increasing with approximately 30% of isolates being resistant. This phenomenon is problematic as therapeutic options for vancomycin-resistant *Enterococcus* (VRE) are limited. Increasing rates of resistance to 3rd-generation cephalosporins were demonstrated in *Escherichia* (*E.*) *coli* and *Klebsiella* (*K.*) *pneumoniae* and increased resistance in *Pseudomonas* (*P.*) *aeruginosa* to imipenem was also observed. Antimicrobial resistance rates are likely to continue to rise in the future. This is of great concern given the relative lack of novel antimicrobial compounds in development.[3]

This review will discuss the common mechanisms of antibiotic resistance, methods to slow the development of resistance, resistance issues with specific gram-positive and gram-negative organisms, and management strategies when infection with resistant bacteria is suspected or confirmed. Neuhauser and colleagues[4] assessed gram-negative resistance in the setting of antimicrobial pressure. Investigators evaluated more than 35,000 isolates between 1994 and 2000 across the United States. The susceptibility of isolates was assessed via minimal inhibitory concentration (MIC) and pathogens originated from the respiratory tract (52%), urine (16%), bloodstream (13.8%), and wounds (11.8%). The organisms responsible for infection included *P. aeruginosa* (n = 8, 244), *Enterobacter* (*E.*) spp (n = 4,999), *K. pneumonia* (n = 4,877), and *E. coli* (n = 4,027). While other antimicrobial agents only suffered a 6% decrease in activity, ciprofloxacin susceptibility for *P. aeruginosa* decreased 21%, from 89% to 68%. It was speculated that this phenomenon was the result of extensive prescribing of fluoroquinolones in both the inpatient and outpatient settings. A strategy to combat this effect has been to restrict fluoroquinolones via infectious disease services. Nseir and colleagues[5] evaluated fluoroquinolone resistance and emerging resistant bacteria in Europe and reported similar findings. A prospective, observational study of 239 patients over a 15-month time period revealed that fluoroquinolone use and duration were independently associated with multidrug-resistant bacteria (MRB) or ([95% CI]) (3.3% [1.7-6.5]) and (1.1 [1.0-1.2]), $P < 0.001$). The overall MRB were higher in the fluoroquinolone group compared with controls, 40% vs. 22%, respectively, $P = 0.028$. Incidentally, the prevalence of MRSA was increased in the fluoroquinolone group compared with controls (26% vs. 12%, $P = 0.028$). The prevalence of extended-spectrum β-lactamase (ESBL)-producing organisms was also greater in

case versus control groups (11% vs. 1%, $P = 0.017$). The MRB rates among *P. aeruginosa* and *Acinebacter* (*A.*) baumannii were not statistically different. Nseir and colleagues demonstrated that MRB emerged with fluoroquinolone use.

Mechanisms of Resistance

Resistance to an antimicrobial may be inherent to bacteria (intrinsic resistance) or may be acquired through genetic mutation or transfer. An example of inherent resistance is cephalosporin resistance in enterococci, which is mediated via penicillin binding proteins for which cephalosporins have decreased binding affinity resulting in minimal activity. Acquired resistance may occur via genetic mutation, (including single point mutations), as well as multiple step mutations, and through transfer of genetic material such as plasmids and transposons.

There are 4 basic mechanisms of antimicrobial resistance: enzymatic inactivation of the antibiotic, decreased antibiotic uptake/accumulation, altered target site, and altered metabolic pathway. Examples of enzymatic inactivation of antimicrobials include β-lactamases, as well as aminoglycoside-modifying enzymes. This mode of resistance causes loss of activity of the antimicrobial via destruction or structural changes. Examples of decreased antibiotic uptake/accumulation include changes in membrane permeability and efflux pumps. Imipenem resistance in *P. aeruginosa* is frequently mediated via alterations in an outer membrane porin, which significantly decreases the ability of imipenem to penetrate the outer plasma membrane and reach its site of action. *P. aeruginosa* is also known to possess drug efflux pumps that are able to actively remove drug from the cytoplasmic and periplasmic spaces. Examples of target site changes include alteration of ribosomes and penicillin binding proteins. Macrolide resistance in *S. pneumoniae* sometimes involves the methylation of the ribosomal target of macrolides. One of the most concerning resistance issues revolves around some organisms such as *P. aeruginosa* and *Acinetobacter* spp, which are able to express several resistance mechanisms making multiple classes of anti-infectives ineffective.

Prevention of resistance

The CDC has developed an excellent program for the prevention of resistance. The CDC's program addresses prevention of resistance via 4 major strategies (Table 1 summarizes these 4 recommendations):

1. Prevent infection.
2. Diagnose and treat infection effectively.
3. Use antimicrobials wisely.
4. Prevent transmission.

Antimicrobial Restriction

Antibiotic use has been associated with the development of resistance.[6] Some investigators have evaluated the effect of antimicrobial restriction on the prevention of resistance. Many of the investigations have taken place as a result of a specific increase in resistance rates of a particular pathogen. Restriction of specific antimicrobials has been uniformly been associated with decreased use of the restricted antimicrobial, and is frequently associated with decreased expenditures, but in regard to decreasing resistance

rates, mixed results have been obtained.[7,8] Rahal and colleagues[9] investigated whether restriction of cephalosporin antibiotics would decrease rates of ESBL-producing *K.* spp. Investigators found that rates of ESBL-producing *K.* spp were decreased; however, with the restriction of cephalosporins, more imipenem was prescribed. As a result, *Pseudomonas (P.) aeruginosa* (PSA) isolates demonstrated increased resistance to imipenem. Overall, decreased resistance in multidrug-resistant gram-negative bacteria was observed. Blanket restriction of specific antimicrobial use has not been shown to definitively reduce overall resistance rates.

Antibiotic Guidelines and Protocols

Another approach to controlling resistance is the use of antibiotic guidelines or protocols. The protocols usually outline appropriate situations for the use of specific antimicrobials, including selection and duration. The antimicrobial is not dispensed unless the clinical scenario matches the approved uses for the antimicrobial. Martin and colleagues[10] reported the results of an antimicrobial restriction policy implemented by the antibiotic subcommittee of pharmacy and therapeutics (P&T) at their institution. The policy was initiated secondary to increasing resistance rates among several organisms, as well as increased antimicrobial expenditures. The antimicrobial subcommittee removed ceftazidime and cefotaxime from its formulary because of the association of these antibiotics with increased rates of gram-negative resistance, as well as increased rates of VRE, and ceftriaxone use was limited to the management of pneumonia, meningitis, and urinary tract infections. Vancomycin use was limited to 72 hours unless the use met the CDC's and Prevention's Hospital Infection Control Practices Advisory Committee (HICPAC) guidelines criteria for appropriate use. If criteria were not met, only an infectious diseases attending could authorize further use of vancomycin. Carbapenem use was also restricted to use in the management of ESBL-producing organisms or in infections secondary to pathogens resistant to alternatives.

Based on the above restrictions, antimicrobial costs were decreased by 25%. Susceptibility of PSA remained relatively constant for most antimicrobials. PSA susceptibility to piperacillin increased over the 5-year period by approximately 3%. This was an interesting finding since there was a 64% increase in the number of defined daily doses per 1000 patient days for piperacillin and piperacillin/tazobactam. The number of multidrug-resistant PSA also decreased.

This analysis demonstrated that an antimicrobial utilization protocol was associated with improved or stable resistance rates and decreased costs. Evidence supports the implementation of protocols and guidelines for the use of antimicrobials. It is recommended to actively involve varied health care providers from multiple disciplines when developing guidelines for antimicrobial use, as compliance with the protocol is improved when health care providers have a part in protocol development.[11]

Double Coverage

Some clinicians have recommended double coverage of gram-negative pathogens as a potential strategy to

decrease the development of resistance. Empiric therapy of infections owing to resistant pathogens presents significant challenges to clinicians. Appropriate empiric therapy should be chosen based on the local susceptibility patterns of the likely infecting organisms. Choosing correct empiric therapy when resistant gram-negative pathogens (e.g., PSA and *A. baumannii*) are suspected as offending pathogens can be problematic. Empiric double coverage of these gram-negative organisms has been proposed as a strategy to improve clinical outcomes.

Double coverage offers 2 potential advantages over monotherapy for empiric gram-negative coverage. The first advantage is simply increasing the likelihood of having at least one active agent against a resistant pathogen. Agents should be from 2 distinct classes of antimicrobials (typically a β-lactam plus an aminoglycoside or fluoroquinolone), so one resistant mechanism is less likely to make both antimicrobials ineffective. Choosing appropriate initial therapy is of utmost importance, as delays in initiating appropriate antimicrobial therapy has been associated with increased mortality for bacteremias and ventilator-associated pneumonia (VAP).[12,13,14] The second rationale behind double coverage is potential for antimicrobial synergy.

Multiple in vitro studies have demonstrated synergistic interaction between antimicrobials against various *P. aeruginosa* and *A. baumannii*. Synergistic activity with 2 agents has been proposed as a mechanism to improve outcomes. Unfortunately, clinical outcome data assessing the benefit of synergy with double coverage have yielded conflicting results.[9] At this time, empiric double coverage for gram-negatives is beneficial at increasing the likelihood of having at least one active agent; however, it is not known if double coverage is superior to monotherapy when susceptibilities are known.

Antimicrobial Cycling

Antimicrobial cycling involves the regular rotation of antimicrobials from different classes with similar spectrum of activity for the management of infection in a particular area of the health care facility. A particular antimicrobial is used for a time period, then is switched to another agent for the next time period. Eventually the cycle will complete itself, and the original antimicrobial will be used again. The theoretical benefit of cycling revolves around the principle that organisms develop resistance to antimicrobials because of exposure. Cycling of the antimicrobials decreases the exposure of the hospital flora to any one antimicrobial. Several investigators have examined cycling. In general, trials investigating cycling have revealed mixed results.[15,16] Currently, insufficient evidence exists to recommend antibiotic cycling as a definitive means to decrease resistance.

Short-Course Therapy

Since antimicrobial exposure has been linked with resistance, ways to decrease exposure may decrease resistance rates. Shorter courses of therapy may provide similar efficacy with less pressure on bacteria. Singh and colleagues[17] conducted a randomized trial comparing outcomes in patients treated in ICUs for pulmonary infiltrates. Patients with clinical pulmonary infection scores (CPIS) of ≤6 were randomized to standard therapy, which consisted of

treatment of the infiltrates at physician discretion or to ciprofloxacin with reevaluation of symptoms at 3 days. If the CPIS score was still ≤6 at 3 days, then antibiotic therapy was discontinued in the intervention group. The authors found that antibiotics were continued with a CPIS score ≤6 beyond 3 days in 96% of patients in the standard group versus 0% of the intervention group (P = 0.0001). Mortality and length of ICU stay were not significantly different between the 2 treatment strategies. Antimicrobial resistance and/or superinfections developed in 15% of patients in the intervention group versus 35% in the standard group (P = 0.017).

This analysis demonstrates the importance of limiting unnecessary antimicrobial therapy. Short-course antimicrobial therapy was associated with similar mortality and length of stay, as well as with decreased development of resistance, antimicrobial costs, and superinfection. Chastre and colleagues[18] conducted a randomized, double-blind trial of patients with VAP comparing 8 days of therapy with 15 days of therapy. Investigators found no significant difference in mortality or infection recurrence that was seen with the treatment groups. However, when subgroup analysis was completed, infection recurrence occurred significantly more frequently in the 8-day therapy group when infection was attributable to a non-fermenting, gram-negative rod. When recurrent infection did develop, patients in the 8-day treatment group were also less likely to have multidrug-resistant pathogens isolated (42.1% vs. 62.0%, P = 0.04). This investigation demonstrated that shorter courses of therapy did not compromise efficacy, and were associated with lower rates of recurrence because of multidrug-resistant pathogens. Dunbar and colleagues[19] examined the effect of high-dose, short-course levofloxacin (750 mg daily for 5 days versus standard dose and treatment course (500 mg daily for 10 days) on outcomes for the management of community-acquired pneumonia (CAP). Clinical cure and microbiologic cure were similar between the 2 groups.

Shortening courses of therapy is an appealing strategy to decrease resistance, as well as cost of therapy; however, more research on other infectious disease conditions will be necessary to prove efficacy before shorter courses of therapy can be used for non-VAP and non-CAP patients.

Maximizing Pharmacokinetics and Pharmacodynamics Properties of Antimicrobials

Repeated exposure to suboptimal concentrations is an important risk factor for the development of resistance.[20] Pharmacokinetic properties involve absorption, distribution, metabolism, and excretion. Pharmacodynamics describe the effect antimicrobials have on organisms and infectious indications. Antimicrobials can be classified based on their pharmacodynamic killing properties. For concentration-dependent antimicrobials, including aminoglycosides and fluoroquinolones, maximum killing is achieved by using optimal peak to MIC ratios. In other words, killing is enhanced as the peak concentration of the antimicrobial increases. For aminoglycosides, peak to MIC ratios should be approximately 8-12 to ensure optimal outcomes.[21] For fluoroquinolones, the area under the curve (AUC) to MIC ratio should be

approximately 125 for gram-negative pathogens, and AUC to MIC ratio should be approximately 25 to 30 for *S. pneumoniae*.[22] For time-dependent (concentration-independent) antimicrobials, including β-lactams, monobactams, and vancomycin, maximum killing is achieved by ensuring antimicrobial concentration is greater than the MIC for the organisms for the majority of the dosing interval.

Other antimicrobials, such as macrolides and tetracyclines, are classified as bacteriostatic. Bacteriostatic agents inhibit the growth of bacteria but do not kill bacteria. For this reason, continuous exposure to concentrations of the antimicrobial above the MIC for the infecting organism is necessary to optimize the effect of bacteriostatic drugs.
Clinicians should consider the pharmacokinetic and pharmacodynamic properties of antimicrobials. For concentration-dependent antimicrobials, increased peak to MIC ratios or AUC to MIC ratios are most important for killing, while length of time above MIC is the most important parameter for time-dependent drugs.

Gram-Positive Organisms

Streptococcus pneumoniae

The Tracking Resistance in the United States Today (TRUST) surveillance program monitors rates of *S. pneumoniae* resistance. For the time period 2001-2002, approximately 18.4% of isolates of *S. pneumoniae* were resistant to penicillin, while approximately 27.5% and 0.9% demonstrated resistance to macrolides and fluoroquinolones, respectively.[23] Penicillin resistance in *S. pneumoniae* is mediated via alterations in penicillin-binding proteins (PBPs). Macrolide resistance is mediated via *mef*A and *erm*B genes, which cause efflux and the methylation of the ribosomal target, respectively. Fluoroquinolone resistance in *S. pneumoniae* is sporadic and has not yet reached a level of great concern in the United States; however, reports of treatment failures are increasing.[24] Fluoroquinolone resistance is mediated via alterations in topoisomerase IV via the *par*C gene and DNA gyrase via the *gyr*A gene. Concerns exist regarding overuse of fluoroquinolones and the development of resistance.

Management of resistant strains of *S. pneumoniae* can be difficult, as resistance to one class of antimicrobial is associated with increased likelihood of resistance to other classes of antimicrobials. For instance, erythromycin resistance is more common in isolates that demonstrate penicillin resistance, and fluoroquinolone resistance is also more frequent in patients with penicillin-nonsusceptible and erythromycin-resistant strains.[25] Fortunately, several therapeutic options exist. High doses of penicillin or amoxicillin may be able to overcome resistance. Also, broader spectrum β-lactams such as ceftriaxone frequently retain their activity. Fluoroquinolone resistance remains an uncommon phenomenon in the United States, which allows fluoroquinolone use for the management of penicillin-resistant and macrolide-resistant isolates. Vancomycin retains activity against 100% of isolates. Another alternative for the management of penicillin-resistant and macrolide-resistant isolates of *S. pneumoniae* is telithromycin. The drug is a ketolide antibiotic with a structure

derived from macrolides. Telithromycin has enhanced binding affinity for its ribosome target, which increases its activity. Quinupristin/dalfopristin, linezolid, and daptomycin are broad-spectrum, gram-positive agents that have activity against *S. pneumoniae*; however, these agents should be reserved for the management of other resistant gram-positive pathogens such as MRSA and VRE, since there are other agents available for the management of resistant *S. pneumoniae.*

Methicillin-Resistant *Staphylococcus aureus* Based on NNIS data, more than 1 out of every 2 isolates of *S. aureus* isolated from the ICU is resistant to methicillin. When initiating empiric therapy for serious infections most likely attributable to *S. aureus*, clinicians should consider the empiric use of vancomycin. Serious infections owing to *S. aureus* with susceptibilities pending should also be managed with vancomycin. Methicillin resistance is coded for in *S. aureus* via the *mec*A gene, which confers a conformation change in PBPs. This change in conformation in PBP prevents the effective binding of all current, commercially available β-lactams resulting in decreased activity. The development of MRSA include the following risk factors:

- Advanced age
- Male gender
- Previous hospitalization
- Increased length of hospitalization
- Stay in an ICU
- Chronic medical illness
- Prior antimicrobial treatment
- Exposure to a colonized or infected patient
- Presence of invasive indwelling devices[26]

Historically, therapy for infections attributable to MRSA has consisted of vancomycin. Vancomycin achieved its primary role as a result of a lack of effective alternative agents. However, vancomycin failures are well documented.[26] Vancomycin poorly distributes to several tissues, including the lungs, central nervous system, and bone. Several new agents have been developed with activity against MRSA.

Quinupristin/dalfopristin (Q/D) is a 30:70 mix of 2 streptogramin antibiotics. Q/D is bacteriostatic against *Staphylococcus* spp. Limited published data exist in regard to the management of MRSA infections with Q/D. Drew and colleagues[27] conducted a compassionate use study evaluating therapy of infections secondary to MRSA that were failing prior therapy. The overall success rate was 71.1% (95% CI, 66.7-84.4). Fagon and colleagues[28] compared the efficacy of Q/D with vancomycin for the management of nosocomial pneumonia in a prospective, randomized, open-label trial. The 2 therapies were found to be equivalent, and subgroup analysis of pneumonia secondary to MRSA demonstrated no significant difference in clinical success between Q/D and vancomycin. It should be noted that the study was not designed to determine equivalency for MRSA pneumonia. Q/D did not demonstrate superior activity over vancomycin in the management of MRSA, and one cannot conclude that the 2 therapies are equivalent for MRSA pneumonia because of the study being underpowered. Currently, limited data support using Q/D for the management

of infection attributable to MRSA. Q/D may be considered an alternative in patients not tolerating vancomycin; however, Q/D therapy is not commonly used secondary to infusion-related side effects.

Another alternative to vancomycin for the management of MRSA is linezolid. Linezolid is an oxazilidinone antibiotic that is bacteriostatic against *Staphylococcus* spp. Several studies have been conducted comparing linezolid with vancomycin. Wunderink and colleagues[29] conducted a retrospective subgroup analysis on *S. aureus* nosocomial pneumonia from 2 randomized, double-blind, placebo-controlled trials evaluating linezolid versus vancomycin for the treatment of hospital-acquired pneumonia (HAP). When Kaplan-Meier survival analysis was completed, linezolid therapy was associated with improved survival compared with vancomycin. One important fact was that more patients in the vancomycin group had cardiac comorbidities and diabetes mellitus. How these imbalances affected overall survival rates is hard to determine. Logistic regression analysis was performed, and linezolid therapy was not found to be statistically significantly associated with improved survival (OR 2.2, 95% CI 1.0-4.8, $P = 0.05$). Interestingly, absence of cardiac comorbidities was associated with improved survival (OR 3.0, 95% CI 1.4-6.6, $P = 0.005$). How the imbalance of cardiac comorbidities affected overall survival is unknown. Kollef and colleagues[30] performed another subgroup analysis of the same trials. The study evaluated outcomes for patients treated with vancomycin versus linezolid who had gram-positive VAP. Again, Kaplan-Meier analysis found a survival benefit to be associated with linezolid therapy. Logistic regression was performed again, and found that therapy with linezolid was associated with improved survival (OR 2.6, 95% CI 1.3-5.1, $P = 0.006$). Absence of cardiac comorbidities did not predict improved survival for the subgroup of MRSA VAP. Therefore, the greatest benefit seems to be for the management of MRSA VAP with linezolid. However, randomized, controlled trial data demonstrating the superiority of linezolid will be required to recommend linezolid over vancomycin for initial-line therapy for MRSA pneumonia. Linezolid has demonstrated similar efficacy to vancomycin in several compassionate use trials.

Daptomycin is a cyclic lipopeptide antibiotic, which is rapidly bactericidal against *Staphylococci*. Daptomycin is only approved for the management of skin and soft tissue infections. Currently, only in vitro data support the use of daptomycin for MRSA; however, the agent's rapid cidality may provide benefit over vancomycin for bacteremias and endocarditis. Enrollment recently closed for a trial comparing daptomycin with vancomycin for the management of bacteremia and endocarditis attributable to methicillin-sensitive and methicillin-resistant *S. aureus*. The results of this trial will provide information if daptomycin's favorable pharmacodynamic characteristics against *S. aureus* will translate into improved patient outcomes.

Currently, vancomycin remains the treatment of choice for the management of infections attributable to MRSA. Linezolid has demonstrated some

promising results in the management of HAP/VAP and surgical-site infections; however, prospective data showing superiority will be required to recommend linezolid as first-line therapy for the management of these infections. Q/D's role in the management of MRSA will likely remain reserved because of limited data and the drug's side effect profile.

Vancomycin-Resistant *Enterococcus*

Several genes may code Vancomycin resistance in *Enterococcus*. These genes, *Van*A-G, code for alterations in the makeup of peptidoglycan. Instead of a D-alanyl-alanine end-terminal, the Van-resistant genes substitute other amino acids for alanine. This change prevents vancomycin from binding to its site of action, thus decreasing activity. Therapeutic options for the management of VRE infection are limited. Current options include Q/D, linezolid, and daptomycin. The available data on the management of infections attributable to VRE are primarily from retrospective compassionate use programs and case reports. Q/D is bacteriostatic against *Enterococcus* spp, and the drug is only active against *E. faecium*. *E. faecalis* isolates are usually inherently resistant to Q/D owing to drug efflux. Moellering and colleagues[31] conducted a prospective compassionate use analysis of Q/D for the management of infections attributable to vancomycin-resistant *E. faecium* with 396 patients in the analysis. Clinical and bacteriologic cure were achieved in approximately 51% of patients. Q/D has reasonable activity against vancomycin-resistant *E. faecium* isolates; however, infusion-related toxicities have limited its use.

Linezolid is also bacteriostatic against *Enterococcus* spp. Similar to Q/D, there are few clinical trials with the drug involving VRE infections. Birmingham and colleagues[32] performed a compassionate use trial evaluating the efficacy of linezolid for the management of infections attributable to VRE. Clinical cure was achieved in 73.3% of patients. Raad and colleagues conducted the efficacy of linezolid and Q/D in a head-to-head trial in 40 cancer patients with VRE infections. No significant difference in efficacy outcomes was seen; however, significantly more individuals in the Q/D group experienced arthralgias ($P < 0.01$).

Daptomycin has limited data published on the management of VRE infections. This agent may have an advantage over linezolid and Q/D, since it is bactericidal against this pathogen. Currently, only in vitro data support the efficacy of daptomycin. Further clinical experience is necessary before recommending daptomycin over linezolid for the management of infection attributable to VRE; however; daptomycin is a reasonable alternative to linezolid in patients who are intolerant to the drug.

Gram-Negative Organisms

Pseudomonas aeruginosa

P. aeruginosa, or PSA, is a gram-negative rod that can be isolated from soil, water, plants, and animals.[33] PSA is generally considered to be a hospital pathogen, but is also associated with community-acquired infections that are frequently associated with exposure to a water source. Several risk factors for infection attributable to PSA have been discovered and include prior antimicrobial therapy, mechanical

ventilation, and extended duration of ICU admission.[34]

Antimicrobial resistance in PSA may be mediated by several mechanisms: β-lactamase production, aminoglycoside-modifying enzymes, alterations in DNA gyrase, efflux pumps, and permeability barriers.[35] Of even greater concern is the ability of PSA to demonstrate resistance to multiple classes of antimicrobials through the expression of multiple resistant mechanisms. PSA efflux pumps can remove antimicrobials from multiple classes greatly limiting therapeutic options. For example, the mexAB efflux pump is effective against fluoroquinolones and β-lactams with the exception of imipenem.[36]

Choosing appropriate empiric therapy for PSA can pose a significant challenge to clinicians. Most experts recommend double coverage with agents from different classes and, as mentioned above, empiric double coverage for PSA increases the likelihood of having at least one active agent. Clinicians should choose the 2 agents for double coverage based on the local antibiogram, site of infection, and other patient-related factors. Studies evaluating the effect of synergy with double coverage on outcomes have yielded mixed results.

When multiple-resistant mechanisms are present, the polymyxins, colistin, and polymyxin B are sometimes the sole antimicrobials that retain activity. Owing to increasing rates of multidrug-resistant PSA, these drugs are experiencing a slight resurgence in use.[37] These agents are associated with significant nephrotoxicity and neurotoxicity, and they should, therefore, be reserved for situations where resistance to safer antimicrobials such as β-lactams, fluoroquinolones, or aminoglycosides is documented. Generally, polymyxin E is preferred over polymyxin B secondary to increased nephrotoxicity associated with polymyxin B.[38]

Acinetobacter baumannii

A. baumannii is a gram-negative rod that is commonly found in soil and water. The organism has also been isolated from multiple sources and surfaces in the hospital setting and has the propensity to remain viable after routine cleaning.[39] Several risk factors for infection with the organism have been elucidated and include length of hospital stay, surgery, wounds, previous infection, use of extended-spectrum β-lactams or carbapenems (independent of previous antibiotic use), fecal colonization with *Acinetobacter*, treatment with broad-spectrum antibiotics, and parenteral nutrition.[40] Resistance in *Acinetobacter* spp may be mediated by altered PBPs, low outer membrane permeability, target site mutations, and inactivation via modifying enzymes such as β-lactamases.[41]

Therapy with a carbapenem has historically been the agent of choice for empiric therapy of infections secondary to *Acinetobacter* spp. However, resistance to carbapenems is increasing. For this reason, double coverage may be considered. Typically, an aminoglycoside or fluoroquinolone is added to the carbapenem; however, resistance to fluoroquinolones and aminoglycosides has also been reported. The sulbactam component of ampicillin/sulbactam has antimicrobial activity against *Acinetobacter* spp, and tetracyclines have also demonstrated activity. A reasonable empiric regimen

for the management of *Acinetobacter* spp would include a carbapenem and an aminoglycoside. Once susceptibilities are known, it is not known if combination therapy is associated with improved outcomes.

Unfortunately, like *P. aeruginosa*, reports of isolates that are resistant to almost all commercially available antimicrobials are increasing. In some cases, only the polymyxins retain activity. Multidrug-resistant *Acinetobacter* infections present a significant dilemma for clinicians. Limited clinical outcome data exist on the most appropriate strategy to manage infections owing to this pathogen. Management of infections attributable to these isolates should be based on local susceptibility patterns.

Extended-Spectrum β-Lactamase–Producing Organisms

Type II extended-spectrum β-lactamases (ESBLs) are most commonly produced by *E. coli* and *K. pneumoniae*.[42] Risk factors for the acquisition of ESBLs include indwelling catheters, prior antibiotic therapy (i.e., ceftazadime), intra-abdominal surgery, and mechanical ventilation (MV).[43] ESBLs are able to hydrolyze most commercially available β-lactams except the carbapenems and cephamycins (cefoxitin, cefotetan, and cefmandole). Patterson and colleagues[44] evaluated the management of bacteremia secondary to ESBL-producing *Klebsiella* spp and observed that patients treated with carbapenems demonstrated improved survival compared with those patients treated with alternative agents. For these reasons, carbapenems have become the mainstay of therapy for ESBL-producing bacteria. Although in vitro susceptibility testing may demonstrate susceptibility to the cephamycins, ticarcillin/clavulanate, piperacillin/tazobactam, and cefepime, these agents are not recommended because of numerous reports of treatment failures. In vitro evidence has shown that ertapenem is stable against ESBLs,[45] but clinical treatment data are lacking; therefore, ertapenem's role in the management of ESBL-producing organisms is yet to be determined. Organisms that produce ESBL can be difficult to manage, since most β-lactams are ineffective and resistance to non-β-lactams such as fluoroquinolones is not uncommon. However, non-β-lactams such as fluoroquinolones, aminoglycosides, and trimethoprim/sulfamethoxazole may be considered for therapy based on susceptibility reports if there are contraindications to carbapenem therapy (e.g., allergy). Aminoglycosides may be used; however, their use is typically limited secondary to associated toxicities. Currently, the agents of choice for ESBLs are the carbapenems. Unfortunately, reports of carbapenem-resistant isolates of *K. pneumoniae* have been reported.[46]

Conclusions

Current surveillance systems demonstrate increasing resistance rates in both gram-positive and gram-negative organisms. Infection with a resistant pathogen increases morbidity, mortality, and hospital costs. Increasing resistance rates have made the task of choosing appropriate empiric therapy difficult. Clinicians must take all appropriate steps to ensure adequate antimicrobial therapy and to minimize the impact of antimicrobial use on resistance by practicing all of the CDC's recommendations.

Figure 1 Resistance Rates NNIS 2003

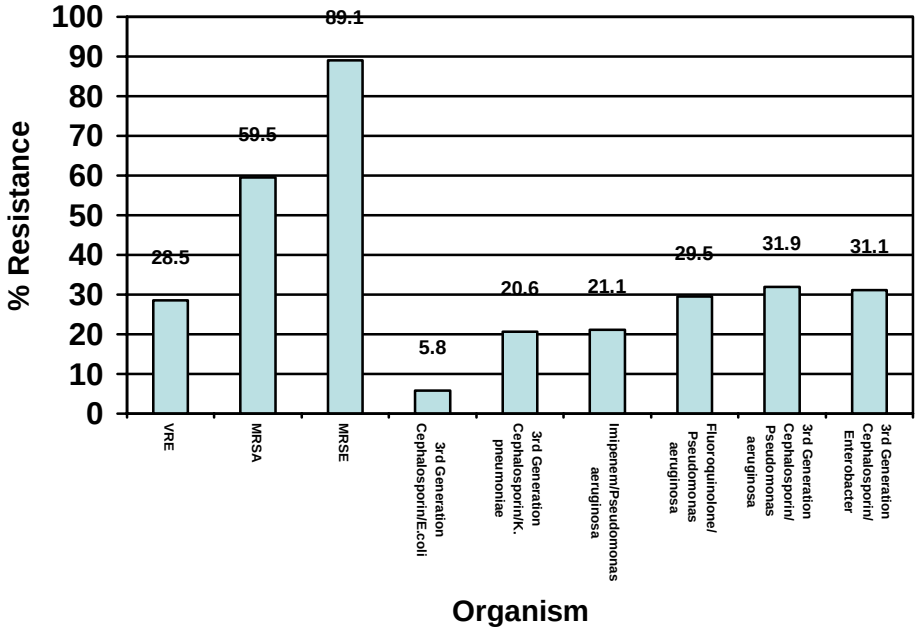

Table 1. CDC's 12 Steps to Prevent Antimicrobial Resistance: Hospitalized Adults[47]
1. Vaccinate -Give influenza/pneumococcal vaccine to at-risk patients before discharge -Get influenza vaccine annually
2. Get the catheters out -Use catheters only when essential -Use the correct catheter -Use proper insertion and catheter care protocols -Remove catheters when they are no longer essential
3. Target the pathogen -Culture the patient -Target therapy to likely pathogens and lock antibiogram -Target definitive therapy to known pathogens and antimicrobial susceptibility test results
4. Access the experts -Consult infectious disease experts for patients with serious infections
5. Practice antimicrobial control -Engage in local antimicrobial control efforts
6. Use local data -Know your antibiogram -Know your patient population
7. Treat infection, not contamination -Use proper antisepsis for blood and other cultures -Culture the blood, and not the skin or catheter hub -Use proper methods to obtain and process all cultures
8. Treat infection not colonization -Treat pneumonia, not the tracheal aspirate -Treat bacteremia, not the catheter tip or hub -Treat urinary tract infection, not the indwelling catheter
9. Know when to say "no" to vancomycin -Treat infection, not colonization or contamination -Fever in a patient with an intravenous catheter is not a routine indication for vancomycin
10. Stop treatment -When infection is cured -When cultures are negative and infection is unlikely -When infection is not diagnosed
11. Isolate the pathogen -Use standard infection control precautions -Contain infectious fluids -When in doubt consult infection control experts
12. Break the chain of contagion -Stay home when you are sick -Keep your hands clean -Set an example

Table 2. Selected Antimicrobial Therapy for Resistant Organisms

Gram-Positive and Gram-Negative Organisms	Selected Antimicrobial Therapy
Streptococcus pneumoniae	Ceftriaxone 1 gram IV q 24h or Vancomycin 15 mg/kg IV q 12h*
Methicillin-Resistant *Staphylococcus aureus* (MRSA)	Vancomycin 15 mg/kg IV q12h* or Linezolid 600 mg IV/PO q12h or Daptomycin 4 to 6 mg/kg IV q24h or Q/D 7.5 mg/kg IV q12h
Vancomycin-Resistant *Enterococcus* (VRE)	Linezolid 600 mg IV/PO q12h or Daptomycin 4 to 6 mg/kg IV q24h or Q/D 7.5 mg/kg IV q8h**
Multidrug-Resistant *Pseudomonas aeruginosa*	Colistin (polymyxin E) 2.5 to 5.0 mg/kg per day (divided into 2 to 4 doses)
Multidrug-Resistant *Acinetobacter baumannii*	Colistin (polymyxin E) 2.5 to 5.0 mg/kg per day (divided into 2 to 4 doses) and/or Ampicillin/Sulbactam 3 grams IV q6h
ESBL-Producing Organisms	Imipenem/cilastin 500 mg IV q6h or Meropenem 1 to 2 gram IV q8

** Q/D will only be effective against *Enterococcus faecium*.

* Vancomycin should be adjusted for trough levels of 15-20 mcg/ml.

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