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Controlling antibiotic resistance in the ICU: Different bacteria, different strategies

ABSTRACT

To reduce antimicrobial resistance in the intensive care unit, hospitals are developing strategies such as improving infection control, adhering to prescribed formularies, requiring prior approval for using certain antibiotics, setting limits on the duration of antimicrobial therapy, and rotating the use of antimicrobial drugs on a regular schedule. Each strategy has theoretical benefits and limitations, but good data on their efficacy in controlling antimicrobial resistance are limited.

KEY POINTS

The emergence and spread of antimicrobial resistance is promoted by two factors: lapses in infection control and antibiotic selective pressure.

To control the spread of methicillin-resistant *Staphylococcus aureus*, infection control is key.

Cephalosporin-resistant (extended-spectrum beta-lactamase) *Klebsiella pneumoniae* is best controlled by limiting the use of extended-spectrum cephalosporins in general and ceftazidime in particular.

In controlling vancomycin-resistant *Enterococcus faecium*, both infection control and wise antibiotic use are important.

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TO CONTROL the rising problem of antibiotic resistance in intensive care units (ICUs), we need to do only two things: enforce infection control policies more stringently and use antibiotics more wisely. But the devil is in the details.

Antimicrobial resistance, especially in ICUs, appears at first to be complicated but is at its heart relatively simple. The two drivers of resistance are antimicrobial selective pressure and the transmission of resistant organisms by health care personnel. Effective infection control techniques are well established, but inconsistently adhered to.

There is considerable interest in managing the use of antibiotics in a manner that reduces antimicrobial resistance. Impediments to the success of these strategies are the complex and often interconnecting patterns of antimicrobial selection and persistent tendencies to overuse antimicrobial agents.

The safety and efficacy of most antibiotics has led to the false perception among many physicians that antimicrobial prescriptions are at worst a neutral therapeutic choice, that the antibiotics may help the patient but will not hurt the patient. Studies have begun to quantify the negative impact of unnecessary antimicrobial prescriptions in the ICU.

This paper summarizes efforts in this important field.

WHY IS RESISTANCE GROWING?

The reasons for increased resistance in the hospital are many.

Hospitalized patients are sicker than in

the past, as many relatively healthy patients who once would have been treated in the hospital are now treated as outpatients. Greater severity of illness often means decreased mobility (increasing the risk for aspiration pneumonia and decubitus ulcers, among other things) and increased use of invasive devices (predisposing to infections of the bloodstream, lungs, and urinary tract).

Antibiotics are often given prophylactically or empirically. The frequent use of immunosuppressive agents to treat cancer and other ailments further increases the risk of severe infections, leading to the understandable (if not always wise) prophylactic or empirical use of antibiotics, in some cases reducing the risk of specific infections at the price of increasing the risk that the infections that do occur will be due to resistant organisms.

Severely ill patients tend to be clustered in ICUs. The relative crowding in these areas promotes the spread of bacteria among patients if appropriate infection control is not practiced. Moreover, with the widespread empirical use of antibiotics, the organisms that are transmitted are more likely to be resistant. As a result, ICUs tend to be "hot spots" for resistance in the modern hospital.[1]

ICUs are 'hot spots' for resistance in the modern hospital

POOR INFECTION CONTROL, SELECTIVE ANTIMICROBIAL PRESSURE

All antimicrobial resistance results from the convergence of only two factors: poor infection control and selective pressure from antimicrobial agents.

The exact importance of either of these factors varies with the setting and the pathogen and is difficult to sort out precisely. Nevertheless, in an era of limited resources, it is worthwhile to try to determine which factors are most important for which organisms, so that resources may be invested wisely.

THREE BACTERIA

Many bacterial pathogens in the ICU can show resistance to antibiotics, and each has unique features that need to be considered in controlling them.

We will look at three pathogens that illustrate the relative importance of infection control and selective antibiotic pressure:

- Methicillin-resistant *Staphylococcus aureus* (MRSA)
- Cephalosporin-resistant (extended-spectrum beta-lactamase [ESBL]) *Klebsiella pneumoniae*
- Vancomycin-resistant *Enterococcus faecium* (VRE).

MRSA: INFECTION CONTROL IS KEY

MRSA strains have emerged as major scourges in ICUs in the United States and now account for more than 50% of *S aureus* strains isolated there (**www.cdc.gov/ncidod/hip/NNIS/ar_surv99.htm**).

Mechanisms of methicillin resistance

Methicillin resistance is due to expression of low-affinity penicillin-binding protein PBP2a, encoded by an acquired determinant on a transposable element (although it has not been shown to be transferable between strains).[2] This presumed rarity of transfer suggests that the primary mechanism of MRSA spread is the transmission of resistant organisms themselves rather than transmission of resistance determinants between members of the same species.

Substantial data now suggest that MRSA does in fact spread through the transmission of individual strains within hospitals and cities, and even between countries.[3,4] These strains are mainly transmitted person to person, and transiently colonized health care workers are probably the primary vectors.

Colonization often precedes infection. The most common sites of colonization are the anterior nares, axillae, and wounds. Colonization of the anterior nares is a particularly important mechanism of transmission in the hospital, and data suggest that shedding is substantially increased during upper respiratory infections.[5]

How to control MRSA

Eliminating colonization has limited value. Since the anterior nares are a major source of MRSA infection, one would think that eliminating nasal colonization would

help control MRSA. Unfortunately, many patients are colonized at other locations as well; moreover, infection may be caused by acquired strains.

One recent study suggested that eradicating nasal colonization with the topical antimicrobial agent mupirocin reduces the rate of infection from endogenous strains, but it does not reduce the overall rate of *S aureus* infections in the postoperative period.[6]

Restricting antibiotics also has limited value. To date, there is only circumstantial evidence implicating the use of specific antibiotics in the emergence and spread of MRSA, and no good data to suggest that reducing the use of antibiotics or antibiotic classes will have a significant impact on MRSA prevalence.

Infection control must be considered the key way to limit the emergence and spread of MRSA. Data from Denmark and the Netherlands suggest that strict infection control precautions on a nationwide basis can virtually eliminate MRSA from entire countries.[7]

The threat of vancomycin resistance in *S aureus*

Two reported cases of high-level vancomycin resistance in MRSA in 2002–2003 raise concern that the primary treatment for MRSA—vancomycin—may become less effective in the years to come.[8] Previously, only intermediate levels of vancomycin resistance had been reported in staphylococci, primarily in patients who had received very long courses of vancomycin.[9,10]

The mechanism of intermediate resistance in these strains involved an expansion of the staphylococcal cell wall. This expansion appears to be a suboptimal situation for staphylococci, evidenced by a high rate of reversion to the susceptible phenotype in vitro and no evidence of spread between patients.

The more recent reports of high-level resistance involve transfer of the VanA vancomycin resistance operon from vancomycin-resistant *E faecalis*.[8] The rapidity with which these determinants have spread in enterococci raise concern that a similar rapid rise may occur in *S aureus*.

ESBL *K PNEUMONIAE*: WISE ANTIBIOTIC USE IS KEY

Extended-spectrum cephalosporins were a major advance in treating gram-negative nosocomial infections. In particular, ceftazidime was an important advance because of its potent activity against *Pseudomonas aeruginosa*.

With widespread use of ceftazidime, however, came the emergence of strains of Enterobacteriaceae, particularly *K pneumoniae*, that were resistant to extended-spectrum cephalosporins.[11]

Mechanisms of cephalosporin resistance

Molecular analysis indicates that this resistance is mediated by mutants of common plasmid-mediated beta-lactamases—in many cases the very beta-lactamases the cephalosporins were created to address. The most common of these narrow-spectrum beta-lactamases are designated TEM-1 and SHV-1.

Many strains of ceftazidime-resistant *K pneumoniae* express variants of TEM and SHV known as extended-spectrum beta-lactamases (ESBLs), which contain one or more point mutations.[11] These mutations typically occur in areas of the enzyme important for binding and hydrolysis of beta-lactam antibiotics, mutations which in most cases open up the active site to allow binding of the bulky cephalosporins.

ESBLs are usually encoded by large, transferable plasmids that also encode resistance to several other classes of antibiotics, most commonly aminoglycosides, trimethoprim-sulfamethoxazole, and tetracyclines.[12,13]

At first, ESBL-producing strains of *K pneumoniae* spread quite rapidly in American ICUs, with one survey reporting a more than threefold increase in resistance to ceftazidime over 3 years.[14] The overall prevalence of ESBL *K pneumoniae* strains has leveled off in US ICUs since the early 1990s and is generally stable at around 10% to 15% (**www.cdc.gov/ncidod/hip/NNIS/ar_surv99.htm**). However, in some hospitals the prevalence is considerably higher, and the prevalence in many areas outside the United States is very high.[15–17]

The most common characteristic of hospitals with problems with ESBL *K pneumoniae*

Colonized health care workers are probably the primary vectors of MRSA

is the heavy use of extended-spectrum cephalosporins, particularly ceftazidime.[13,18] In chronic care settings such as nursing homes, fluoroquinolones have also been implicated in infection with ESBL *K pneumoniae*, probably because, for reasons yet to be explained, many of these strains are resistant to fluoroquinolones.[19]

How to control ESBL *K pneumoniae*

The association of ESBL *K pneumoniae* with extended-spectrum cephalosporins in general and ceftazidime in particular suggests that the best way to control these pathogens is to reduce the use of these antibiotics. In fact, several institutions with problems with ESBL *K pneumoniae* have substantially reduced the prevalence of these strains by reducing the use of cephalosporins.[13,18,20,21]

For this purpose, it does not appear to make much difference what antibiotics are substituted for cephalosporins. Both carbapenems and beta-lactam–beta-lactamase inhibitor combinations have been successful. However, imipenem-resistant *Acinetobacter baumannii* and *Pseudomonas aeruginosa* have increased when imipenem was substituted for ceftazidime.[20,22]

For ESBL *Klebsiella pneumoniae*, it does not matter what drugs are substituted for cephalosporins

As might be expected from the presence of ESBL genes on transferable plasmids, outbreaks of ESBL *K pneumoniae* are typically polyclonal, suggesting that antimicrobial selective pressure is important in promoting their spread.[13] However, within polyclonal outbreaks, spread of clonally related strains can usually be found, and spread of individual strains of ESBL *K pneumoniae* has been documented between hospitals.[15] Therefore, it is prudent to emphasize infection control in aborting ESBL *K pneumoniae* outbreaks.

However, in at least one outbreak the prevalence of ESBL *K pneumoniae* was significantly reduced by limiting cephalosporin use alone,[13] suggesting that limiting exposure to this class of antibiotic is of primary importance in controlling continued spread.

VRE: BOTH INFECTION CONTROL AND WISE ANTIBIOTIC USE ARE KEY

One of the more dramatic examples of the spread of antibiotic resistance is that of VRE in the late 1980s. Even though vancomycin was introduced in 1958, VRE was not recognized until 1986. But by 1999, rates of vancomycin resistance in *E faecium* in US ICUs were approaching 25%, where they remain today (**www.cdc.gov/ncidod/hip/NNIS/ar_surv99.htm**).

Mechanisms of vancomycin resistance: Different in VRE and MRSA

Early studies suggested that VRE spreads through hospitals much like MRSA, offering some hope that strict infection control would limit its spread.[23,24]

However, on a molecular level VRE and MRSA are quite different in that the operons conferring vancomycin resistance in enterococci (VanA and VanB) are encoded by transposons that are freely transferable among enterococcal strains.[25,26] Moreover, enterococci colonize the human gastrointestinal tract, which is frequently exposed to high concentrations of antimicrobial agents and an ever-changing microbial flora.

Perhaps predictably, as the VRE outbreak matured, reports suggested that infection control measures and attempts to control vancomycin usage had only limited effectiveness in controlling the spread of VRE.[27]

Molecular analysis indicated that multiple strains of VRE were appearing in the more mature VRE outbreaks, suggesting that enterococcal strains were frequently exchanging genetic material and that antibiotic selective pressure was exerting a strong influence over the spread of VRE.

The antibiotics most commonly implicated in VRE colonization and infection are extended-spectrum cephalosporins and agents with potent activity against anaerobic bacteria. Donskey et al[28] examined the influence of these antibiotics in a mouse model of VRE colonization and found that ceftriaxone (and potentially other extended-spectrum cephalosporins) and ticarcillin-clavulanic acid promote high levels of VRE colonization after inoculation of small numbers of VRE (100 colony-forming units) into the animals' stomachs.

Neither cephalosporins nor ticarcillin show in vitro activity against clinical VRE strains in the United States, the vast majority

of which exhibit high-level beta-lactam resistance through expression of low-affinity PBP5. Expression of this low-affinity PBP confers particularly high levels of resistance to ceftriaxone and ticarcillin (minimum inhibitory concentration [MIC] > 10,000 µg/mL) and lower levels of resistance to ampicillin and piperacillin (MIC 200–1,000 µg/mL).[29]

Therefore, piperacillin, which suppresses establishment of VRE in the Donskey animal model, may do so because it achieves biliary concentrations that exceed the VRE MIC, whereas ceftriaxone and ticarcillin cannot achieve inhibitory levels.

Using a different animal model, Donskey et al also showed that a common characteristic of antibiotics that promote persistence of high levels of VRE stool colonization is potency against anaerobic bacteria.[30] Under these circumstances, antibiotics such as piperacillin-tazobactam promote persistence of VRE colonization, whereas cephalosporins with minimal antianaerobic activity, such as cefepime, do not.

When these studies were extended to humans, exposure to antianaerobic antibiotics clearly increased the output of VRE in previously colonized patients.[31]

To complicate matters, lapses in infection control are also important in the spread of VRE. Bonten et al[32] identified "colonization pressure" (the percentage of VRE-colonized patients in an ICU) and percentage of days on cephalosporin therapy as independent risk factors for early colonization with VRE in ICU patients. The colonization pressure was the more important of the two factors, but cephalosporin exposure was particularly important during times of low colonization pressure.

Therefore, infection control lapses and antimicrobial exposure act in a synergistic and complex fashion to promote the emergence and spread of VRE in the ICU.

STRATEGIES FOR CONTROLLING RESISTANCE

As the above discussion suggests, it will be difficult to devise a single comprehensive strategy for minimizing all resistance in the ICU.

Infection control

Infection control measures that are often used to combat the spread of resistant bacteria in the ICU include efforts to promote handwashing compliance, isolation, cohorting of staff or patients, general or selective surveillance culturing, and decolonization protocols.[33]

Education programs to constantly remind health care providers of their role in preventing transmission of infectious diseases are critical, as are appropriate physical environments and adequate staffing.

Wise antibiotic use: More controversial

More controversial are proposed strategies to use antimicrobial prescribing practices to minimize resistance. Proposed strategies fall into three general categories:

- Restricted formularies or approval policies
- Antimicrobial cycling
- Programmed termination of antimicrobial therapy.

Restricted formularies or approval policies

The use of antimicrobial agents can be restricted at several levels.

Restricted formularies. The pharmacy can restrict availability simply by adhering to a formulary of defined agents.

Severely restricted formularies have limited appeal, however, since patients can become sicker or die if they do not receive effective antimicrobial therapy promptly.[34,35] Given the relatively high prevalence of resistance in many hospitals, it is often difficult to restrict antimicrobial use to one class.

Neither cephalosporins nor ticarcillin show in vitro activity against VRE

Moreover, most formulary restriction policies are based on cost rather than a specific intent to limit resistance, so the effectiveness of such policies for limiting resistance is difficult to know (with the exception of limiting cephalosporins such as ceftazidime during outbreaks of ESBL *K pneumoniae*).

Although high-volume use of antimicrobial agents generally is associated with emergence of resistance to those agents, this effect is neither linear nor predictable.

For example, vancomycin was in use for 25 years before the first cases of VRE were reported, the emergence of which was likely prompted by use of oral vancomycin to treat *Clostridium difficile*. Once VRE emerged, its

spread was promoted by the use of extended-spectrum cephalosporins and antianaerobic agents. If one were to limit all antibiotics that have been associated on some level with VRE, *all* antibiotics would have to be limited.

ESBL *K pneumoniae* is clearly related to the overuse of ceftazidime and is best treated with carbapenems. On the other hand, in vitro and clinical data support ceftazidime as the antibiotic least likely to select resistance in *P aeruginosa*, while imipenem is the antibiotic most likely to select resistance.[36] Inhibitor combinations such as piperacillin-tazobactam have an appeal in this setting. However, the ability of bacteria to overcome the effect of the inhibitor by expressing larger quantities of beta-lactamase or by producing beta-lactamases resistant to inhibition raises questions about the wisdom of relying heavily on these agents for empiric therapy in the ICU.[37]

Prior approval programs. Antibiotic availability can also be restricted by requiring prior approval before using certain agents. The person granting approval would, it is hoped, be someone familiar with the issues of resistance, such as a pharmacist or an infectious disease practitioner.

Most formulary restriction policies are to control cost, not resistance

In a program described by White et al,[38] infectious disease physicians were assigned to 24-hour beeper coverage to consider approval of the use of designated expensive broad-spectrum antibiotics. The primary goal of the program was to reduce antimicrobial costs, although hospital susceptibility data were also gathered as a secondary outcome.

The program was considered a success in that the calculated cost savings exceeded the cost of the program by a substantial sum. Use of the restricted antibiotics was significantly reduced, with concomitant increases in the use of unrestricted antibiotics.

Gram-negative bacilli became more susceptible to the restricted antibiotics over the course of the study, primarily in isolates from the ICU; these included *Escherichia coli*, *K pneumoniae*, *Enterobacter* species, *P aeruginosa*, and *A baumannii*. Increased susceptibilities to nonrestricted antibiotics were also observed, however, raising questions about whether factors other than restriction of antibiotics contributed to increased susceptibilities.

Other studies have also suggested that prior-approval programs can reduce antimicrobial costs, but their impact on rates of resistance has not been consistently demonstrated.[39]

To be effective, prior-approval programs must use significant resources, primarily the dedicated time of pharmacists and infectious disease attending physicians. These programs cannot be easily assigned to fellows in training. Gross et al[39] compared recommendations proffered by an expert antibiotic management team during normal business hours with those proffered by infectious disease fellows after hours and on weekends and found that the fellows' recommendations were inferior to those of the management team by several outcome measures.

A limitation inherent in prior-approval programs is that they place an "uninvolved" practitioner between the primary doctor and his or her patient. Correctly or incorrectly, many physicians have strong opinions about the appropriate therapy to be given in critical situations. The person at the interface between the management team and the primary caretakers must command sufficient respect and possess substantial political skills to avoid creating resentment.

Antibiotic cycling programs

The hypothesis underlying antimicrobial cycling programs is simple: if you keep an antibiotic on the formulary for only a limited time, you can move on to another agent before the resident flora of a hospital or unit within a hospital "wises up" and becomes resistant.

Although several papers have described the effects of switching from one antibiotic or group of antibiotics to another, few data are available on the long-term impact of scheduled rotations on resistance.

Gruson et al[40] compared a "before period" in which ceftazidime plus ciprofloxacin was widely prescribed as empirical therapy for ventilator-associated pneumonia, and an "after period" in which these drugs were rarely used. The susceptibility rates of *P aeruginosa* to various antibiotics improved: susceptibility to piperacillin-tazobactam improved from 62.9% before to 72.3% after, cefepime 53.2% to 74.5%, imipenem 69.3% to 76.6%, and ciprofloxacin 61.3% to 78.7%. Ciprofloxacin

use fell eightfold in the "after period," while piperacillin-tazobactam use increased almost fourfold.

Raymond et al[41] set up a rotating protocol using ciprofloxacin, piperacillin-tazobactam, imipenem-meropenem, and cefepime for empirical treatment of pneumonia and peritonitis or sepsis of unknown origin in a surgery-trauma ICU. Each drug was used for 3 months. Significant reductions occurred in the incidence of antibiotic-resistant gram-positive coccal infections, antibiotic-resistant gram-negative bacillary infections, and mortality associated with infection in the 1-year rotation period compared with the year before. However, infection control practices changed and an antibiotic surveillance team was set up during the study period, complicating the interpretation of these results.

Difficulties with cycling programs. Several theoretical and practical considerations may limit the efficacy of cycling programs.

- The frequency of multiresistance and the possibility of selection of specific pathogens by several classes of antibiotics (as seen with VRE and ESBL *K pneumoniae*) may well make it difficult to create antimicrobial cycles that will not select for the same resistant pathogens as the prior cycle.
- The prevalence of some pathogens, notably MRSA, may not be affected by antimicrobial manipulations.
- No one knows the optimal duration of a cycle or whether it will be the same for all pathogens.
- It may be possible to implement such a program in a well-managed ICU, but since many of the resistant pathogens in the ICU are brought in from elsewhere in the hospital,[42] controlling antibiotic usage within the ICU may not be enough.

It is hoped that ongoing rotation studies sponsored by the Centers for Disease Control and Prevention will provide some answers to these questions.

Programmed termination of antimicrobial therapy

Strategies involving "streamlining" antimicrobial agents after defined periods of time have been tried in several forms.

Fraser et al[43] performed a study in which patients receiving any of 10 designated antibiotics were randomized to continue the therapy or to receive recommendations from an antibiotic team consisting of an infectious disease fellow and a pharmacist. The intervention group incurred a lower antimicrobial cost, demonstrating the ability of streamlining strategies to reduce expenditures.

As with prior-approval studies, however, studies of streamlining offer little compelling information about impact on antimicrobial susceptibility patterns.

Singh et al[44] recently reported a more aggressive streamlining approach in the treatment of presumed ventilator-associated pneumonia. Ventilator-associated pneumonia was defined in this study by the "clinical pulmonary infection score."

Patients with a high score (≥ 6), indicating highly probable ventilator-associated pneumonia, were treated with antibiotics at the discretion of their physicians. Patients with suspected ventilator-associated pneumonia who did not reach this threshold score were randomized to antibiotic therapy with a single antibiotic for just 3 days (39 patients) or antibiotic therapy for a duration chosen by the treating team (42 patients, mean duration of antibiotic therapy 9.8 days).

The patients in the 3-day, single-antibiotic group had significantly fewer superinfections with antibiotic-resistant organisms. The 30-day mortality rate was 13% in the 3-day group vs 31% in the control group ($P = .06$).

These data suggest that overtreating patients who are not infected may be as bad as inadequately treating truly infected patients. In other words, *antimicrobial agents are not at worst a therapeutically neutral choice*.

Under these circumstances, it becomes ever more important to determine, as best as possible, the likelihood that a patient truly has a bacterial infection. If that likelihood is deemed high, broad initial coverage is clearly indicated. If not, narrow empiric coverage is preferred.

In either instance, continued attention to the clinical setting is critical, with as much emphasis placed on discontinuing components of the antimicrobial regimen as on adding to it.

Right or wrong, many physicians have strong opinions about what drug to use

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