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ANTIMICROBIAL RESISTANCE IN INTENSIVE CARE UNITS

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As the treatment of many patients shifts from the hospital setting to home or other alternative health care settings, health care delivery in the intensive care unit (ICU) continues to face new and difficult challenges. First, this shift in patient care has caused an increase in the severity of illness among patients receiving care in the hospital compared with hospitalized patients of the previous decade. This shift may partially explain the changes in hospital demographics among hospitals participating in the Centers for Disease Control and Prevention's (CDC's) National Nosocomial Infections Surveillance (NNIS) System. Data from NNIS shows a 17% increase in the number of ICU beds at the hospitals from 1988 to 1995, whereas total hospital bed capacity has decreased slightly (Fig. 1).[2] Second, patients who receive care in ICUs are at increased risk for nosocomial infections, especially pneumonia, urinary tract infection, and bloodstream infection.[17] Third, the emergence of antimicrobial-resistant pathogens in ICUs has made treating these infections very difficult and, in some cases, impossible. This article reviews important aspects of the ICU environment that contribute to infections with antimicrobial resistant bacteria, summarizes rates of resistance in the most common pathogens associated with nosocomial infections among ICU patients, and provides an overview of strategies to prevent the proliferation of antimicrobial-resistant bacteria.

FACTORS IN INTENSIVE CARE UNITS PROMOTING ANTIMICROBIAL RESISTANCE

Cross-Transmission

Several factors unique to ICUs contribute to cross-transmission of antimicrobial-resistant pathogens. First, the urgent nature of critical care often does not allow for necessary aseptic technique or handwashing. Second, evidence suggests antimicrobial-resistant pathogens are carried from patient to patient (exogenous flora) via the unwashed hands of health care workers.[19] The large number and wide variety of health care workers attending to patients' needs have inconsistent training and compliance with hand washing, gloving, and gowning. Third, specific agents used for hand washing, the degree of asepsis used in maintaining invasive devices, and the level of crowding in ICUs may impact on the cross-transmission of these pathogens as well.[11, 15, 24, 36] Finally, the introduction of antimicrobial-resistant bacteria into an ICU may occur upon transfer of critically ill patients unknowingly colonized or infected with such bacteria from other facilities.

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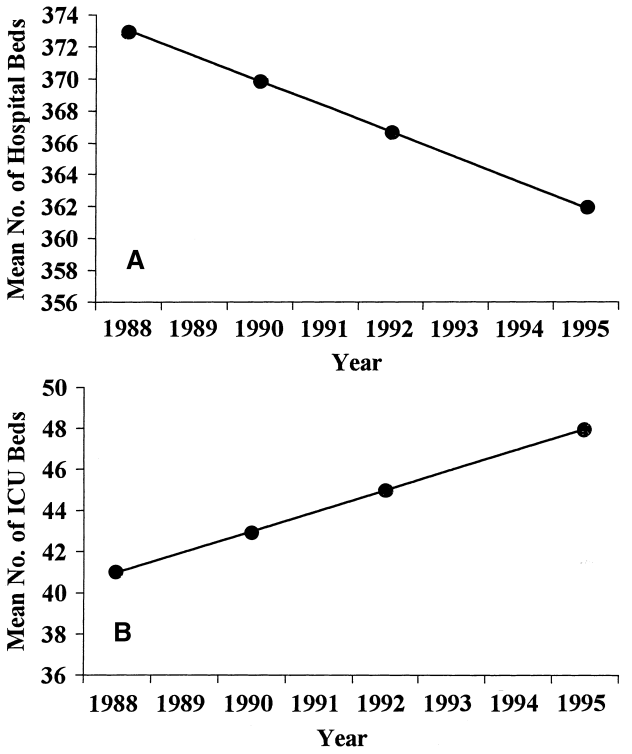

Figure 1. Results of five surveys of 70 hospitals participating in the National Nosocomial Infections Surveillance (NNIS) system from 1988 through 1996; the survey examined the total number of licensed beds and the relative number of intensive care unit (ICU) beds. *A*, A plot of the mean number of total hospital beds by year that fits a regression line. *B*, A similar plot of the mean number of NNIS ICU beds by year. Although there was a decrease in the mean number of total hospital beds during this period, it was not significant. In contrast, the increase in the number of NNIS ICU beds was statistically significant ($P<.05$). (*From* Archibald L, Phillips L, McGowan JE Jr, et al: Antimicrobial resistance in hospitals and outpatients in the United States: The increasing importance of the intensive care unit. Clin Infect Dis 24:211–215, 1997; with permission.)

Host Defense

Colonization of ICU patients with antimicrobial-resistant pathogens can lead to clinical infection because of breakdown of normal host defenses. ICU patients are particularly susceptible to nosocomial infection because the normal skin and mucosal barriers to infection are commonly compromised by the use of invasive devices. It is no surprise that the incidence of nosocomial infection in ICU patients is correlated with the use of invasive devices.[28] In addition, ICU patients often have severe underlying illnesses, suppressed immune systems, malnutrition, and a history of frequent hospitalization. These types of patients may be more likely than otherwise healthier patients to be (1) colonized or infected with an antimicrobial-resistant pathogen from exposures during a previous health care encounter, and (2) exposed to antimicrobial agents before hospitalization in the ICU. All of these factors—especially the need to use antimicrobial agents in ICU patients (as discussed subsequently)—contribute to the increased risk of developing nosocomial infections with antimicrobial-resistant pathogens.[7, 18, 21, 41, 60]

Antimicrobial Use

Perhaps no other factor is more important in the development of antimicrobial resistance than antimicrobial use.[9, 41, 42, 55] Many studies have demonstrated a correlation be-

tween antimicrobial use and antimicrobial resistance at the hospital level.[54, 59] Of studies involving hospital-acquired pathogens, 22 reviewed by McGowan[38] showed a fairly consistent association between use and resistance. Unfortunately, nearly all of these studies were reports from single hospitals, which may not be representative of other hospitals. A previous multicenter study in the 1970s, however, demonstrated that changes in aminoglycoside use paralleled changes in aminoglycoside-resistant gram-negative bacilli.[20] One other multicenter study also demonstrated this type of relationship among several antimicrobials and the corresponding resistant pathogens, including ceftazidime use and ceftazidime-resistant *Enterobacter cloacae*.[3]

RATES OF ANTIMICROBIAL RESISTANCE IN INTENSIVE CARE UNITS

Gram-Positive Pathogens

Table 1 shows the eight most common pathogens associated with nosocomial infections among ICU patients from January 1989 through June 1998. The relative frequency of each of these pathogens (or pathogen groups) is influenced by the site of infection and the type of ICU, where type of ICU is an indirect measure of case mix.[49, 50] Each of the pathogens listed has demonstrated antimicrobial resistance to at least one, if not several, of the antimicrobial agents commonly used to treat infections caused by these pathogens.

In general, gram-positive organisms (i.e., *Staphylococcus aureus*, coagulase-negative staphylococci, enterococci) are commonly associated with central line-associated bloodstream or surgical site infection (see Table 1).[17] Examination of the rates of antimicrobial resistance among these pathogens shows that rates of methicillin-resistant *S. aureus* (MRSA) and methicillin-resistant coagulase-negative staphylococci have increased steadily over the past decade (Fig. 2*A*, *B*). Perhaps in response to the increasing numbers of infections with MRSA, which requires treatment with vancomycin, there has been a dramatic rise in the percentage of enterococcal isolates resistant to vancomycin—from 0.5% in 1989 to 22% in 1997 among ICU patients with nosocomial infection reported to NNIS (Fig. 2*C*). These data also illustrate the importance of the ICU in rates of antimicrobial resistance. For each of the gram-positive organisms evaluated, the rates of resistance were significantly higher in patients cared for in the ICU than in non-ICU patients (Table 2).

Gram-Negative Pathogens

Gram-negative bacilli are frequently associated with nosocomial infections in ICU patients, particularly ventilator-associated pneumonia and catheter-associated urinary tract infections (see Table 1).[17] Of particular concern is the nosocomial infection caused by enterobacteria-producing extended-spectrum β-lactamases (ESBLs), particularly *Klebsiella pneumoniae*. Organisms that possess these enzymes are usually resistant to multiple antimicrobials and hydrolyze third-generation cephalosporins and aztreonam, rendering

Table 1. EIGHT MOST COMMON PATHOGENS ASSOCIATED WITH NOSOCOMIAL INFECTION IN AN INTENSIVE CARE UNIT PATIENT, NATIONAL NOSOCOMAL INFECTIONS SURVEILLANCE SYSTEM, JANUARY 1989–JULY 1998

	Relative Percentage by Site of Infection					
Pathogen	All sites n = 235,758	BSI n = 50,091	PNEU n = 64,056	UTI n = 47,502	SSI n = 22,043	Other n = 52,066
Coagulase-negative staphylococci	14.3	39.3	2.5	3.1	13.5	15.4
Staphylococcus aureus	11.4	10.7	16.8	1.6	12.6	13.7
Pseudomonas aeruginosa	9.9	3.0	16.1	10.6	9.2	8.7
Enterococci spp.	8.1	10.3	1.9	13.8	14.5	5.9
Enterobacter spp.	7.3	4.2	10.7	5.7	8.8	6.8
Escherichia coli	7.0	2.9	4.4	18.2	7.1	4.0
Candida albicans	6.6	4.9	4.0	15.3	4.8	4.3
Klebsiella pneumoniae	4.7	2.9	6.5	6.1	3.5	3.5
Others	30.7	21.8	37.1	25.6	26	37.7
Total	100	100	100	100	100	100

BSI = laboratory confirmed (primary) bloodstream infection; PNEU = pneumonia; UTI = urinary tract infection; SSI = surgical site infection.

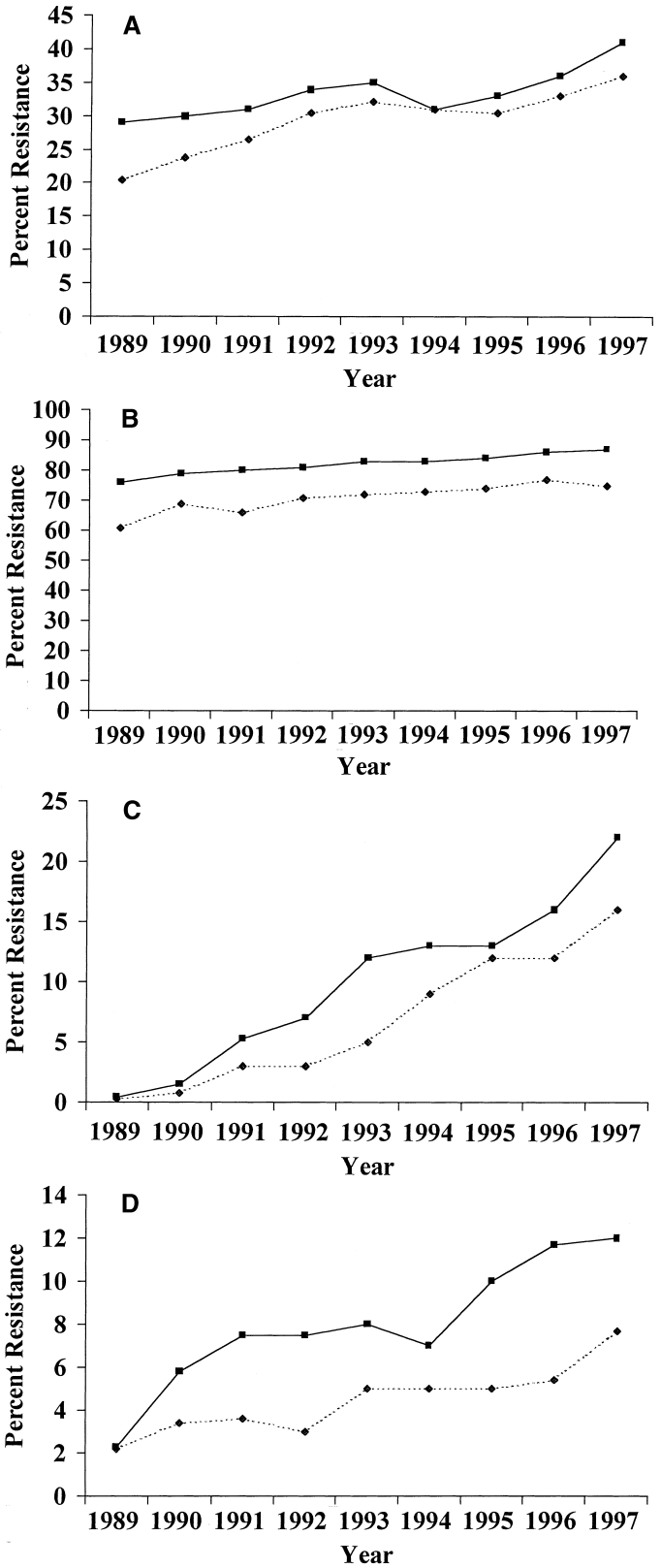

Figure 2. Proportion of isolates associated with a nosocomial infection among ICU *(solid line)* or non-ICU *(dotted line)* patients who were *A*, *S. aureus* resistant to methicillin; *B*, coagulase-negative staphylococci resistant to methicillin; *C*, enterococci resistant to vancomycin; *D*, *Klebsiella pneumoniae* resistant to third-generation cephalosporins (i.e., ceftriaxone, cefotaxime, or ceftazidime);

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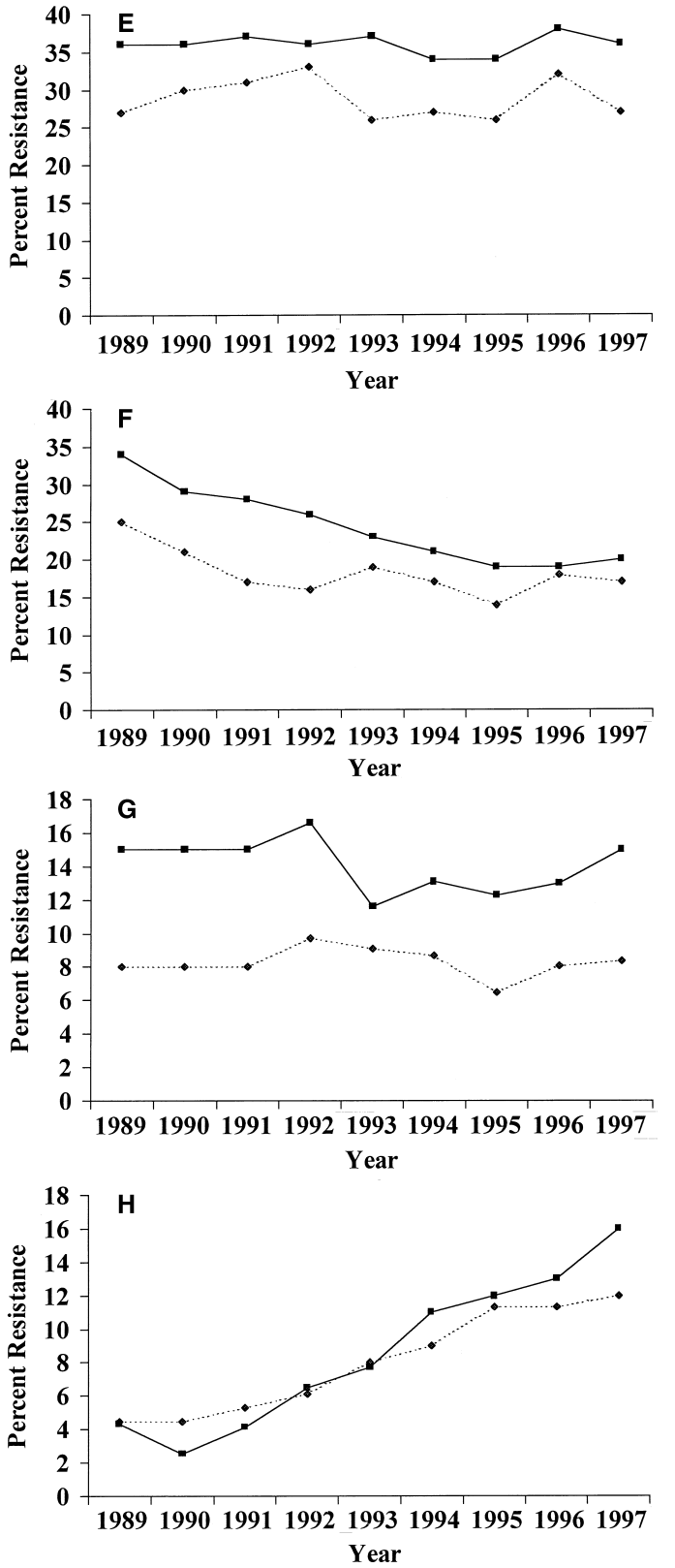

Figure 2 *(Continued). E, Enterobacter* spp. resistant to third-generation cephalosporins; *F, P. aeurginosa* resistant to third-generation cephalsoporins; *G, P. aeruginosa* resistant to imipenem; and *H, Pseudomonas aeruginosa* resistant to ofloxacin or ciprofloxacin. National Nosocomial Infections Surveillance System, January 1989–June 1998.

Table 2. RELATIVE RISK OF ISOLATING THE SPECIFIC ANTIMICROBIAL-RESISTANT PATHOGEN FROM A NOSOCOMIAL INFECTION OCCURRING IN AN INTENSIVE CARE UNIT PATIENT COMPARED WITH OTHER PATIENTS, NATIONAL NOSOCOMAL INFECTIONS SURVEILLANCE SYSTEM, JANUARY 1989–JULY 1998

Pathogen	Antimicrobial Resistance	Relative Risk Among ICU Patients (95% CI)*
Coagulase-negative staphylococci	Methicillin	1.22 (1.21–1.24)
Staphylococcus aureus	Methicillin	1.09 (1.07–1.16)
Enterococci spp.	Vancomycin	1.16 (1.13–1.20)
Enterobacter spp.	Third-generation cephalosporins	1.11 (1.09–1.13)
Klebsiella pneumoniae	Third-generation cephalosporins	1.24 (1.20–1.30)
Pseudomonas aeruginosa	Imipenem	1.16 (1.13–1.21)
Pseudomonas aeruginosa	Third-generation cephalosporins	1.13 (1.11–1.16)
Pseudomonas aeruginosa	Ciprofloxacin/ofloxacin	1.03 (1.00–1.05)

**Data from* NNIS system, common relative risk and 95% confidence interval, by Mantel-Haenszel Statistic, controlling for year of infection.

these potent antibacterial agents useless.[48] In some cases, ceftriaxone or cefotaxime may test susceptible or intermediate to ESBL-producing *K. pneumoniae*, but the clinical utility of these agents against such isolates is uncertain, and clinical failures have been reported.[31, 48]

Evaluation of data from NNIS hospitals shows a dramatic increase in the proportion of *K. pneumoniae* resistant to ceftriaxone, cefotaxime, or ceftazidime over the past decade, with a much greater increase among isolates recovered from ICU patients (see Fig. 2*D*, Table 2). The prevalence of ESBL-producing strains is easily underestimated because resistance to β-lactam agents, although increased, may fail to reach currently specified resistance breakpoints.[26] Tracking resistance patterns therefore may not be ideal for detecting ESBL-producing enterobacteria (e.g., some ESBL-producing *K. pneumoniae* may test intermediate to third-generation cephalosporins). Tracking resistance, as in Figure 2*D*, however, provides us with a rough estimate of the growing magnitude of this troublesome pathogen.

Duration of stay in the hospital, especially the ICU, has been associated with acquisition of ESBL-producing *K. pneumoniae*[8, 45, 53] and has been implicated in inter-facility transmission within a geographic region.[40] There is strong evidence that antimicrobial exposure has an impact on the acquisition of ESBL-producing *K. pneumoniae*. One study[48] demonstrated that preferential use of a specific β-lactam/β-lactamase inhibitor combination (i.e., piperacillin/tazobactam) rather than ceftazidime was associated with a decrease in rates of isolating these organisms in the ICU. Another[47] demonstrated that patients exposed to any β-lactam/β-lactamase inhibitor combination (i.e., amoxicillin/clavulanic acid, ampicillin/sulbactam, ticarcillin/clavulanic acid, or piperacillin/tazobactam) appeared to be at decreased risk of colonization or infection with ESBL-producing *K. pneumoniae* in multivariate analysis. This suggests that preferential use of β-lactam/β-lactamase inhibitor combinations may be an important control measure, along with hand-washing and infection control precautions, to help control outbreaks of ESBL-producing *K. pneumoniae*.

Other common antimicrobial-resistant pathogens encountered among ICU patients include *Pseudomonas aeruginosa* resistant to imipenem and *P. aeruginosa* or *Enterobacter* spp. resistant to third-generation cephalosporins, such as cefotaxime, ceftriaxone, or ceftazidime. Examination of data from NNIS hospitals shows that rates of resistance among these pathogens again appear higher among isolates from ICU patients compared with non-ICU patients (see Fig. 2*E–G*, Table 2). The rates of resistance have been relatively stable over the past decade, however. Ampicillin-resistant *Escherichia coli* is of less concern to the ICU clinician because alternative therapy is readily available and these patients are commonly on a broad-spectrum agent to which the organism is susceptible.

Finally, the rate of fluoroquinolone resistance (i.e., resistance to ofloxacin or ciprofloxacin) among *P. aeruginosa* reported to NNIS has increased rapidly over the past decade (Fig. 2*H*). In contrast to all the other pathogens discussed so far, however, quinolone-resistant *P. aeruginosa* is not more prevalent among ICU patients compared with non-ICU patients (see Table 2). There are probably many reasons for this. Contributing factors

may include the large amounts of quinolones used by patients outside the ICU, or the development of fluoroquinolone resistance among *P. aeruginosa* unrelated to the ICU setting.[37]

Candida

Candida albicans is the seventh most common pathogen associated with nosocomial infection in ICU patients (see Table 1). In general, resistance to antifungal agents among *Candida* spp. is rare. Susceptibility testing for *C. albicans* is difficult and not routinely performed in most hospitals, however, so data on the frequency of fluconazole-resistant *C. albicans* tend to be limited to research scenarios.[47] Therapeutic options to treat patients with *C. albicans* infection include polyenes (amphotericin), imidazoles, and triazoles. The emergence of antimicrobial-resistant fungal pathogens limits the few therapeutic options. Some acquired immunodeficiency syndrome patients, particularly those with greater exposure to azole therapy or low CD4 counts, have developed azole-resistant *C. albicans* infections.[29, 35] Resistance to azoles has not been well documented in human immunodeficiency virus-negative patients. The appearance of azole-resistant *C. albicans* infection in AIDS patients portends resistance in other immunocompromised patient populations. Data suggest that increasing use of prophylactic antifungal therapy in patients at highest risk for endogenous *Candida* spp. infection may lead to the increasing frequency of infections with fungi such as *C. krusei*, which have intrinsic azole-resistance, or the even azole-resistant *C. glabrata* or *C. albicans*.[1, 14, 29, 35] Consequently, issues relating to azole-resistant *Candida* spp. will usually be limited to the specialized care unit exclusively treating patients with a severely compromised immune system. Of concern are data from a recent multicenter study of 50 U.S. medical centers that documented that 10% of *C. albicans* isolates from the bloodstream of hospitalized patients were resistant to fluconazole.[44] The resistant rate ranged from 5% to 15%, depending on the region of the United States, suggesting that local factors, such as amount of azole usage, may play a role in the relative frequency of azole-resistant *C. albicans* infections.

EVALUATING ANTIMICROBIAL USE IN INTENSIVE CARE UNITS

When evaluating the relative rates of different antimicrobial agents used in the hospital, total grams may be misleading. Because different agents have different potency, researchers often standardize amounts of antimicrobials used by referring to the *defined daily dose* (DDD), which is the grams an average person will receive in a day (for vancomycin, 1 DDD = 2 g). By dividing the actual grams by the DDD, comparisons between different agents of differing potency can be made with more validity. The actual DDD values may vary among studies and should be published with each study. Furthermore, the total amount of antimicrobials used in a hospital or an ICU will be confounded by the number of patients in the hospital or ICU each day. Accurate comparisons of antimicrobial use among ICUs or hospitals therefore should evaluate the rate of use (i.e., DDD per 1000 patient-days).

Data from Project ICARE, a study assessing antimicrobial use and resistance at a subset of 41 hospitals participating in the NNIS system, show that use is significantly higher among ICU patients than non-ICU patients for third-generation cephalosporins combined, ceftazidime alone, intravenous vancomycin, antipseudomonas penicillin, intravenous fluoroquinolones, or imipenem (Fig. 3).[16] There is no significant difference between ICU and non-ICU areas in use of antistaphylococcal penicillin (i.e., methicillin group), first-generation cephalosporins, second-generation cephalosporins, or aztreonam (see Fig. 3). Significantly lower rates of use were reported in adult ICU areas for trimethoprim/sulfamethoxazole, oral vancomycin, or oral fluoroquinolone. If oral and parenteral fluoroquinolone use was combined, however, rates of usage were similar between ICU and non-ICU areas.

This observation lends support to the hypothesis presented earlier that the reason rates of quinolone-resistant *P. aeruginosa* are similar among nosocomial infections in ICU patients compared with non-ICU patients (see Fig. 2*H*) is that the exposure to quinolones may be similar in both parts of the hospital. In summary, for each of the antimicrobial groups used at higher rates in ICU areas, there was a correspondingly higher rate of the respective resistant pathogens among ICU

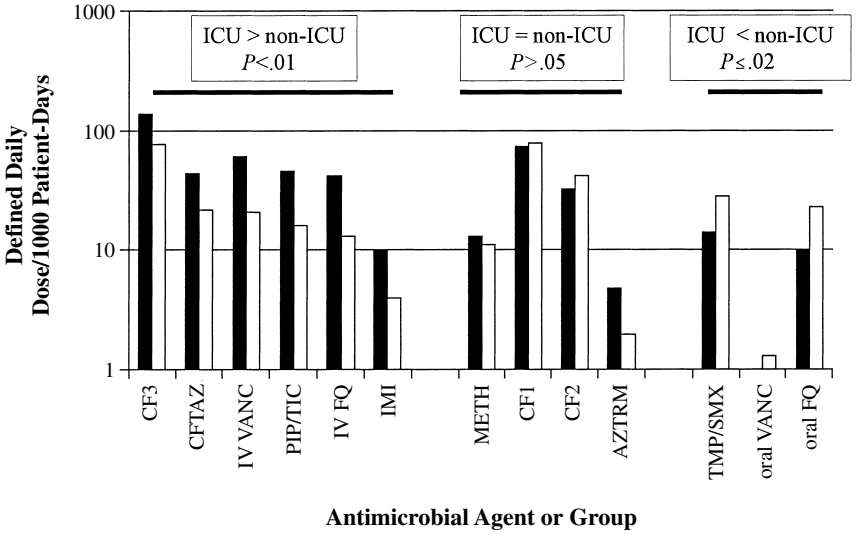

Figure 3. Comparison of median rates of antimicrobial use (i.e., defined daily doses per 1000 patient-days) reported in adult ICUs (n = 108) and non-ICU areas combined (n = 40). All use is for intravenous antimicrobials and oral (where applicable), except where noted. CF3 = third-generation cephalosporins (ceftriaxone, cefotaxime, ceftazidime, and ceftizoxime); CFTAZ = ceftazidime; VANC = vancomycin; PIP/TIC = antipseudomonal penicillins (piperacillin, piperacillin/tazobactam, ticarcillin, ticarcillin/clavulanic acid); FQ = fluoroquinolones (ofloxacin and ciprofloxacin); IMI = imipenem; METH = methicillin group (oxacillin, nafcillin, methicillin); CF1 = first-generation cephalosporins (cefazolin, cephalothin); CF2 = second-generation cephalosporins (cefotetan, cefoxitin, cefuroxime); AZTRM = aztreonam, TMP/SMX = trimethoprim/sulfamethoxazole. Solid bar = ICU patients; open bar = non-ICU inpatients.

patients compared with non-ICU inpatients among hospitals reporting data to ICARE (Table 4).

PREVENTING THE EMERGENCE AND SPREAD OF RESISTANT BACTERIA IN INTENSIVE CARE UNITS

Optimizing Use of Antimicrobial Agents

A workshop sponsored by the CDC and the National Foundation for Infectious Diseases recommended that hospitals should monitor antimicrobial use in an attempt to reduce the emergence and spread of antimicrobial-resistant pathogens.[22] Such monitoring also can aid the infection-control team in determining how to focus its efforts in reducing the emergence and spread of antimicrobial-resistant pathogens.[56] Most importantly, controlling antimicrobial resistance (and use) is a multifaceted problem requiring a multidisciplinary approach.[27]

Data Collection and Feedback

One method to optimize use includes providing feedback data to ICU clinicians. Such data will help clinicians make wise empiric therapy choices and provide direction in altering antimicrobial choice in efforts to reduce specific problems with resistance. One study demonstrated that rates of antimicrobial resistance may differ among specific types of ICUs and that feedback to clinicians on ICU-specific rates of resistance leads to changes in antimicrobial selection and subsequent reduction in the ICU-specific resistance rates.[59] Feedback regarding antimicrobial use may be necessary as well.

Comparative Data

Hospitals may use comparative data, such as those provided by Project ICARE, to determine whether specific ICUs or the entire hospital is overusing antimicrobials. Caution must be used in making any comparisons of antimicrobial use data because antimicrobial use depends on the types of patients cared for in the ICU. Data from Project ICARE illustrate that different types of ICU use different amounts of specific antimicrobials (Table 3).

Table 3. POOLED MEANS AND PERCENTILES OF ANTIMICROBIAL USE IN DEFINED DAILY DOSES PER 1000 PATIENT-DAYS, REPORTED FROM 20 CORONARY CARE UNITS, 19 MEDICAL INTENSIVE CARE UNITS, 27 MEDICAL/SURGICAL UNITS, 12 CARDIOTHORACIC UNITS, AND 19 GENERAL-SURGICAL UNITS, JANUARY 1996–DECEMBER 1997, PROJECT ICARE: PRELIMINARY ANALYSIS

Type of ICU	Antimicrobial or Antimicrobial Group	Rate of Use (DDD/1000 Patient-Days)				
				Percentiles		
		Total DDD	Pooled Mean	10%	50%	90%
Coronary (n = 20 ICUs)						
	Ampicillin group	2335	38.1	5.8	41.3	92.8
	Anti-pseudomal penicillin group	1491	24.4	0.5	15.0	92.0
	Methicillin group	1219	19.9	0.0	13.2	44.0
	First-generation cephalosporins	5615	91.7	9.1	39.5	330.5
	Second-generation cephalosporins	2982	48.7	2.7	21.3	61.1
	Third-generation cephalosporins	5296	86.5	21.2	87.3	171.7
	Imipenem	394	6.4	0.0	3.2	24.7
	Aztreonam	389	6.4	0.0	1.3	14.6
	Ciprofloxacin	2277	37.2	0.0	30.6	97.3
	Trimethoprim/sulfamethoxazole	1710	27.9	0.0	14.0	82.2
	Vancomycin (parenteral)	2141	35.0	9.2	25.6	108.9
Medical (n = 19 ICUs)						
	Ampicillin group	6692	115	39.4	96.9	206.6
	Anti-pseudomonal penicillin group	5103	87.6	2.7	80.3	180.1
	Methicillin group	1492	25.6	0.7	20.4	46.2
	First-generation cephalosporins	1925	33.1	17.1	33.5	70.3
	Second-generation cephalosporins	3121	53.6	7.2	51.0	102.0
	Third-generation cephalosporins	12,129	208	74.8	173.7	382.5
	Imipenem	1439	24.7	0.0	16.7	54.5
	Aztreonam	431	7.4	0.0	5.4	24.1
	Ciprofloxacin	3629	62.3	0.6	50.6	117.0
	Trimethoprim/sulfamethoxazole	2792	47.9	0.0	35.5	95.7
	Vancomycin (parenteral)	4939	84.8	27.4	59.1	157.2
Medical-Surgical (n = 27 ICUs)						
	Ampicillin group	11,414	92.2	30.1	98.1	160.7
	Anti-pseudomonal penicillin group	7240	58.5	19.8	46.7	100.0
	Methicillin group	2829	22.8	0.0	14.3	60.5
	First-generation cephalosporins	15,480	125	30.2	85.1	257.8
	Second-generation cephalosporins	8539	69.0	7.4	47.4	103.9
	Third-generation cephalosporins	23,961	194	94.0	200.7	322.1
	Imipenem	3858	31.2	0.7	25.0	66.3
	Aztreonam	1664	13.4	0.2	8.5	36.2
	Fluoroquinolone group	9945	80.3	9.6	64.4	134.9
	Trimethoprim/sulfamethoxazole	5051	40.8	0.0	23.2	95.5
	Vancomycin (parenteral)	8379	67.7	25.6	53.2	134.2
Cardiothoracic (n = 12 ICUs)						
	Ampicillin group	959	27.1	5.3	25.7	45.8
	Anti-pseudomonal penicillin group	989	28.0	0.7	22.5	51.0
	Methicillin group	397	11.2	0.0	2.4	18.6
	First-generation cephalosporins	9596	271	74.6	305.0	465.4
	Second-generation cephalosporins	1898	53.6	0.7	20.5	141.1
	Third-generation cephalosporins	2942	83.1	16.5	74.6	120.7
	Imipenem	523	14.8	0.0	4.5	37.5
	Aztreonam	313	8.9	0.0	0.9	7.8
	Fluoroquinolone group	1692	47.8	7.8	31.4	86.2
	Trimethoprim/sulfamethoxazole	345	9.7	0.0	3.4	13.6
	Vancomycin (parenteral)	4606	130	24.8	85.6	198.0
General-surgical (n = 19 ICUs)						
	Ampicillin group	5968	109	49.8	97.5	197.9
	Anti-pseudomonal penicillin group	3456	62.9	2.9	58.0	138.8
	Methicillin group	1489	27.1	1.6	14.2	50.3
	First-generation cephalosporins	11,635	212	94.7	195.2	557.2
	Second-generation cephalosporins	3283	59.8	21.3	53.3	103.4
	Third-generation cephalosporins	9089	165	95.6	142.8	249.8
	Imipenem	1880	34.2	0.0	18.4	66.3
	Aztreonam	713	13.0	1.4	10.9	36.1
	Fluoroquinolone group	4015	73.1	25.9	69.1	122.4
	Trimethoprim/sulfamethoxazole	1961	35.7	1.7	17.9	68.7
	Vancomycin (parenteral)	6439	117	42.0	87.6	207.5

DDD = Defined daily doses.

Third-generation cephalosporins (cefriaxone, cefotaxime, ceftazidime, and ceftizoxime), first-generation cephalosporins (cefazolin, cephalothin), second-generation cephalosporins (cefotetan, cefoxitin, cefuroxime), anti-pseudomonal penicillin group (piperacillin, piperacillin/tazobactam, ticarcillin, ticarcillin/clavulanic acid), fluoroquinolone group (ofloxacin and ciprofloxacin), methicillin group (oxacillin, nafcillin, methicillin).

Table 4. SUMMARY OF RATES OF ANTIMICROBIAL-RESISTANT PATHOGENS AND USE OF THE ANTIMICROBIAL AGENTS ASSOCIATED WITH RESISTANCE IN THE INTENSIVE CARE UNIT AREAS COMPARED WTIH NON-INTENSIVE CARE UNIT AREAS, PROJECT ICARE, PHASE 2, 1996–1997

Higher Resistance in ICUs Compared with Non-ICU Areas	Higher Use in ICUs Compared with Non-ICU Areas
E. coli, P. aeruginosa: ceftazidine	Third-generation cephalosporins or ceftazidime
P. aeruginosa: piperacillin	Ureido/carboxy penicillins
Enterococci: vancomycin	Vancomycin
Similar or Less Resistance in ICUs Compared with Non-ICU Areas	**Similar or Less Use in ICUs Compared with Non-ICU Areas**
Pneumococcus: penicillin	Aminopenicillins
E. coli, P. aeruginosa: quinolones	Quinolones

We therefore report use rates by specific type of ICU back to ICARE hospitals. Accounting for the type of ICU, when an ICU is using a specific antimicrobial at a rate beyond the 90th percentile, evaluating how and why that usage is so high may help optimize use.

Patterns of Use

After an institution determines that it is overusing antimicrobials, a detailed examination of patterns is needed. Antimicrobial use can be divided into three categories—empiric therapy, definitive therapy, and prophylaxis. Each aspect of therapy may need to be addressed by different means to achieve any benefit. Surprisingly, only about 30% of all antimicrobials in hospitals are used for definitive therapy in which the susceptibility patterns for the infection-associated pathogen are known.[10] The problem behind a specific ICU's excessive use of an antimicrobial may result from misuse within any or all of the three categories.

Most data on reducing inappropriate use of antimicrobials have involved vancomycin.[13, 30, 52, 57, 61] These studies documented 30% to 80% of empiric and 20% to 25% of definitive vancomycin therapies were inappropriate. It may be necessary to implement antimicrobial control programs tailored to the areas of most inappropriate use or greatest amount of use to optimize use. For instance, one study demonstrated that most vancomycin use occurred during the first 3 days of therapy, and that focusing efforts on improving initial empiric therapy reduced inappropriate use greatly.[57]

Interventions

Efforts to improve antimicrobial use in hospitals have generally focused on cost-saving interventions,[32, 51] although some studies have documented decreased rates of colonization or infection with antimicrobial-resistant bacteria after interventions.[14, 39, 62] These interventions usually include some restriction policy on specific antimicrobial agents, with or without other mechanisms, such as automatic stop orders after 72 hours of empiric use.[56] A recent study by White et al[62] demonstrated that preapproval for selected parenteral agents reduced rates of antimicrobial-resistant pathogens without compromising patient outcomes, with the greatest effect occurring within ICUs. In another study, rates of vancomycin-resistant enterococci were reduced when vancomycin use was reduced.[46] In general, however, the efficacy of specific aspects of programs to improve antimicrobial use remains unclear and their effectiveness in reducing antimicrobial resistance has been difficult to assess.[39] In addition, implementation of either criteria-based guidelines (i.e., appropriate versus inappropriate use) or diagnosis-based guidelines (e.g., community-acquired pneumonia) have been promulgated by professional societies. Their effectiveness in optimizing antimicrobial use has not yet been determined, but appears promising.

Preventing Cross-Transmission

Hand Washing

Hand washing is considered the single most important measure for preventing the spread of infection in hospitals.[19, 33] Hands should be washed between patient contacts, after contact with potentially infectious material (e.g., blood, body fluids, patient-care items), and after removal of examination gloves. Although CDC recommends hand washing with bland soap to be sufficient in most settings,[19] there is evidence that routine hand antisepsis may be helpful in reducing rates of nosocomial infections and spread of

antimicrobial-resistant bacteria in ICU settings.[11, 12, 25, 33] This measure is recommended in areas in which vancomycin-resistant enterococci may be endemic.[25]

Several studies have shown poor compliance with, and quality of, hand washing by health care workers.[11, 23, 34, 36] These studies illustrate that various interventions to improve hand washing have had limited success, including use of automatic sinks, new emollient soap, antiseptic hand rub solution, or chlorhexidine-containing soap. As a measure to control cross-transmission, many ICUs have supplemented conventional antiseptic hand washing with alcohol-based hand rubs, which may be particularly useful when and where hand washing facilities are inaccessible.[33] The efficacy of these agents in reducing rates of infections with antimicrobial-resistant bacteria (and infections with *Candida* spp.) needs to be assessed.

Gloves

Glove use, in addition to hand washing, has been shown to decrease the spread of bacteria between patients and health care workers and among patients.[43] Glove use, however, has not been shown to be a replacement for hand washing. The ''Standard Precautions'' described in the CDC's guidelines for isolation precautions in hospitalized patients include routine glove use when touching blood, body fluids, secretions, excretions, and contaminated items, with removal of gloves and hand washing promptly after use. In addition, routine glove use may be appropriate in certain settings. In an ICU in which resistant bacteria (i.e., multiresistant *Staphylococcus aureus* or vancomycin-resistant enterococci) behave as commensal skin flora[4, 5]; for example, routine wearing and changing of gloves between patient contacts may prevent hand contamination and transmission after touching intact, but contaminated, skin of patients or contaminated environmental surfaces.

Gowns

The use of gowns as an added barrier has been recommended for years to help control the spread of MRSA within hospitals.[6, 19] Evidence of their efficacy in controlling the spread of other antimicrobial-resistant pathogens is less well developed. In one study of a medical ICU in a large urban hospital, gowns were found to offer no benefit beyond that afforded by gloves in controlling the spread of endemic vancomycin-resistant enterococci.[58] CDC does recommend gowns for substantial contact with patients who are colonized or infected with vancomycin-resistant enterococci, however.[25] In some settings, such as neonatal units, routine gown use may be required by local public health or hospital policy, but such recommendations should be avoided unless based on documented evidence of local need and efficacy in controlling the spread of pathogens.

Face Masks

Personal respirators are used to protect health care workers from infection by patients with pulmonary tuberculosis. The use of these when caring for patients with pulmonary infections caused by antimicrobial-resistant bacteria is unlikely to affect the risk for cross-infection.[19]

Patient Isolation or Cohorting

Isolating or cohorting patients with known infections or colonization by antimicrobial-resistant bacteria is an effective means of controlling patient-to-patient transmission. Isolation recommendations for clinical syndromes and for specific pathogens have been published by CDC and the Society for Healthcare Epidemiology of America.[19, 25, 56] In decisions about when to cohort patients colonized or infected with an antimicrobial-resistant pathogen, surveillance cultures are useful in determining the extent of the cohort. The patients should remain isolated (or in a cohort) until adequate therapy for the infection is instituted and the patient is no longer a carrier.

Traffic Control

An often overlooked and understudied aspect of infection control is the importance of minimizing movement of personnel through ICUs. Ancillary staff from respiratory therapy, nutritional support, pharmacy, consultative services, anesthesiology, and radiology pass in and out of ICUs frequently, which may increase the risk of cross-infection from other parts of the hospital or within the ICU. ICU directors and staff should consider devel-

oping traffic guidelines for ICUs and should ensure that all personnel who spend time working in the ICU have the necessary infection-control education.

CONCLUSION

Several considerations must be kept in mind when evaluating antimicrobial resistance in the ICU setting. The magnitude of the problem cannot be determined without knowledge of a hospital's (or an individual ICU's) pattern of antimicrobial use. Dramatic differences in antimicrobial resistance exist within individual hospitals and may depend on both antimicrobial use and infection control practices. Only by improving surveillance of antimicrobial resistance and antimicrobial use can hospitals begin to make rational decisions about allocating scarce resources toward improving patient care by reducing rates of infection with antimicrobial-resistant bacteria. No strategy for controlling resistance or optimizing antimicrobial use will be successful unless the entire health care delivery system views this problem as vital. A multidisciplinary, systems-oriented approach involving the hospital leadership is required to succeed in combating the growing problem of antimicrobial resistance in ICUs.[22]

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