# International Study of the Prevalence and Outcomes of Infection in Intensive Care Units

Jean-Louis Vincent, MD, PhD
Jordi Rello, MD
John Marshall, MD
Eliezer Silva, MD, PhD
Antonio Anzueto, MD
Claude D. Martin, MD
Rui Moreno, MD, PhD
Jeffrey Lipman, MD
Charles Gomersall, MD
Yasser Sakr, MD, PhD
Konrad Reinhart, MD
for the EPIC II Group of Investigators

**Context** Infection is a major cause of morbidity and mortality in intensive care units (ICUs) worldwide. However, relatively little information is available about the global epidemiology of such infections.

**Objective** To provide an up-to-date, international picture of the extent and patterns of infection in ICUs.

**Design, Setting, and Patients** The Extended Prevalence of Infection in Intensive Care (EPIC II) study, a 1-day, prospective, point prevalence study with follow-up conducted on May 8, 2007. Demographic, physiological, bacteriological, therapeutic, and outcome data were collected for 14 414 patients in 1265 participating ICUs from 75 countries on the study day. Analyses focused on the data from the 13 796 adult (>18 years) patients.

**Results** On the day of the study, 7087 of 13 796 patients (51%) were considered infected; 9084 (71%) were receiving antibiotics. The infection was of respiratory origin in 4503 (64%), and microbiological culture results were positive in 4947 (70%) of the infected patients; 62% of the positive isolates were gram-negative organisms, 47% were gram-positive, and 19% were fungi. Patients who had longer ICU stays prior to the study day had higher rates of infection, especially infections due to resistant staphylococci, *Acinetobacter*, *Pseudomonas* species, and *Candida* species. The ICU mortality rate of infected patients was more than twice that of noninfected patients (25% [1688/6659] vs 11% [682/6352], respectively; $P<.001$), as was the hospital mortality rate (33% [2201/6659] vs 15% [942/6352], respectively; $P<.001$) (adjusted odds ratio for risk of hospital mortality, 1.51; 95% confidence interval, 1.36-1.68; $P<.001$).

**Conclusions** Infections are common in patients in contemporary ICUs, and risk of infection increases with duration of ICU stay. In this large cohort, infection was independently associated with an increased risk of hospital death.

*JAMA. 2009;302(21):2323-2329* www.jama.com

INFECTION IS A COMMON PROBLEM FOR patients in intensive care units (ICUs) and is associated with considerable morbidity, mortality, and costs.[1-4] Infection and related sepsis are the leading cause of death in noncardiac ICUs, with mortality rates that reach 60% and account for approximately 40% of total ICU expenditures.[1,5] Importantly, the incidence of sepsis is increasing, as is the number of consequent infection-related deaths.[3,6]

Most large epidemiologic studies of infection and sepsis have been conducted in North America, Europe, and Australia,[1,6-11] with limited data from other countries.[12,13] Differing definitions and different study populations make it difficult to compare study results. International data related to the prevalence, risk factors, causative microorganisms, and outcomes of infection are necessary to increase and maintain awareness of the impact of infection, to help in the development of local and international guidelines for diagnosis and treatment, to facilitate adequate and appropriate resource allocation, and to assist in the design of multicenter interventional studies.

The European Prevalence of Infection in Intensive Care (EPIC) study,[14] conducted on April 29, 1992, included data from 1417 ICUs in 17 Western European countries and provided valuable information regarding the prevalence and epidemiology of infection in critically ill European patients. Fifteen years after that successful international collaboration, the Extended Prevalence of Infection in Intensive Care (EPIC II) study was conducted to provide an up-to-date picture of the extent and patterns of infection in ICUs around the world.

**For editorial comment see p 2367.**

## METHODS

An international steering committee was established in 2006 and selected the study date, May 8, 2007. Intensive care units were invited to participate in a 1-day, prospective, multicenter point prevalence study of ICU infection. Methods for recruitment of participating institutions included direct mailings to members of the European Society of Intensive Care Medicine, an-

**Author Affiliations** are listed at the end of this article.
**Corresponding Author:** Jean-Louis Vincent, MD, PhD, Department of Intensive Care, Erasme University Hospital, Route de Lennik 808, B-1070 Brussels, Belgium (jlvincen@ulb.ac.be).
**Caring for the Critically Ill Patient Section Editor:** Derek C. Angus, MD, MPH, Contributing Editor, *JAMA* (angusdc@upmc.edu).

nouncements at international meetings and symposia, and mailings to contacts and collaborators of each steering committee member. Participation in the study was entirely voluntary, and the study was not funded. Local ethical committee approval at each participating center was expedited or waived owing to the purely observational nature of the study.

Demographic, physiological, bacteriological, and therapeutic data were collected from all patients present in a participating ICU between midnight on May 7 and midnight on May 8, 2007. Simplified Acute Physiology Score II (SAPS II)[15] and Sequential Organ Failure Assessment (SOFA)[16] scores were calculated for the study day. Data were recorded using preprinted case report forms and submitted via a dedicated Web site (90% of centers), by fax, or by mail. Data were not monitored. Participating ICUs were asked to provide patient follow-up until hospital discharge or for 60 days (until July 9, 2007), and ICU and hospital outcomes were recorded. Any decision to withdraw or withhold therapy during the ICU stay was also noted. A dedicated telephone hotline was available for any queries during the study follow-up period. Centers with missing data were contacted regularly in an attempt to obtain complete data, but any data still missing at closure of the database were simply noted as absent; there was no imputation of missing data.

Infection was defined according to the definitions of the International Sepsis Forum[17] and adjudicated by the attending physician. Patients who had undergone surgery in the 4 weeks preceding admission were considered surgical admissions. Elective surgery was defined as surgery scheduled more than 24 hours in advance, and emergency surgery as that scheduled within 24 hours of operation. Trauma admissions were defined as ICU admissions directly related to, or occurring as a complication of, a traumatic event in the 30 days preceding admission. All other admissions were considered medical.

The presence of the following comorbid conditions was noted: chronic obstructive pulmonary disease; metastatic cancer (metastases confirmed by surgery or imaging techniques); liver cirrhosis; heart failure (New York Heart Association class III-IV); hematologic malignancy (lymphoma, acute leukemia, or multiple myeloma); human immunodeficiency virus (HIV) infection (HIV-positive patients with clinical complications such as *Pneumocystis jirovecii* pneumonia, Kaposi sarcoma, lymphoma, tuberculosis, or toxoplasmosis); chronic renal failure (need for chronic renal support or history of chronic renal insufficiency, with a serum creatinine level greater than 3.6 g/dL [300 µmol/L]); immunosuppression (administration of steroid treatment in the 6 months prior to ICU admission [at least 0.3 mg/kg per day of a prednisolone equivalent for at least 1 month], severe malnutrition, congenital immunohumoral or cellular immune deficiency state); chemotherapy/radiotherapy (in the 6 months prior to ICU admission); insulin-dependent diabetes mellitus (need, prior to ICU admission, for insulin administration to control blood glucose levels).

### Statistical Analyses

All data were analyzed in the Department of Intensive Care of the University of Brussels, Belgium, in collaboration with the University of Jena, Germany. Statistical analyses were performed using SPSS version 13.0 (SPSS Inc, Chicago, Illinois). For the purposes of this article, only data from adult (>18 years) patients were analyzed, and the world was divided into 7 geographical regions: North America, Central and South America, Western Europe, Eastern Europe, Asia, Oceania, and Africa.

The Kolmogorov-Smirnov test was used, and histograms and normal-quantile plots were examined, to verify if there were significant deviations from the normality assumption of continuous variables. Nonparametric tests of comparison were used for variables evaluated as not normally distributed. Difference testing between groups was performed using analysis of variance, Kruskal-Wallis test, *t* test, Mann-Whitney test, $\chi^2$ test, and Fisher exact test, as appropriate. A Bonferroni correction was made for multiple comparisons.

Multivariate logistic regression analysis was used to determine risk factors for infection and hospital mortality. The following variables were investigated as independent risk factors for infection: type of admission, source of admission, comorbid conditions, age, sex, mechanical ventilation, hemofiltration or hemodialysis, and SAPS II score. The same variables plus infection were investigated as risk factors for hospital mortality. The multivariate analysis with hospital mortality as the dependent variable was repeated for infected patients, including type of microorganism as an additional risk factor.

Odds ratios were adjusted for hospital- and organizational-related factors, including type of ICU (closed vs open, community vs university, surgical vs medical), number of ICU beds, number of nurses, number of physiotherapists, presence of 24-hour ICU physician coverage, percentage of gross domestic product spent on health care (obtained from the World Health Organization [http://www.who.int/whosis/whostat/EN_WHS09_Full.pdf], generated using the World Health Organization Statistical Information System and based on data from 2006), length of ICU stay prior to study day, and geographical region. A Cochran-Armitage trend test was used to analyze the association between the rate of infection and percentage of gross domestic product spent on health care, SAPS II and SOFA scores, and duration of ICU stay before study date. Data are presented as mean (95% confidence interval), median (interquartile range [IQR]), or number (%) as appropriate. All statistics tests were 2-tailed, and $P < .05$ was considered statistically significant.

## RESULTS

### Characteristics of Total Study Group

EPIC II recruited 1265 ICUs in 75 countries: 667 ICUs in Western Europe, 210 in Central and South America, 137 in Asia, 97 in Eastern Europe, 83

in North America, 54 in Oceania, and 17 in Africa (see eAppendix at http://www.jama.com for list of participating ICUs). The greatest number of patients came from Western Europe. Sixty percent of the participating ICUs were in university hospitals, 66% were mixed medical-surgical ICUs, and 94% had 24-hour ICU physician coverage. Characteristics of the ICUs are presented in eTable 1.

On the study day, 14 414 patients were present in 1 of the participating ICUs; 13 796 were older than 18 years, and their demographic characteristics are presented in TABLE 1. Sixty-two percent of the patients were men, 62% were surgical admissions, and 52% had at least 1 comorbid condition.

## Prevalence and Characteristics of Infections

Of the 13 796 adult patients, 7087 (51%) were classified as infected on the day of the study. Seventy-one percent of all patients were receiving antibiotics (as prophylaxis or treatment). Of the infected patients, 16% were being treated with antifungal agents. Infected patients had more comorbid conditions and higher SAPS II and SOFA scores on admission than noninfected patients (Table 1). The lungs were the most common site of infection, accounting for 64% of infections, followed by the abdomen (20%), the bloodstream (15%), and the renal tract/genitourinary system (14%) (TABLE 2).

Seventy percent of infected patients had positive microbial isolates: 47% of the positive isolates were gram-positive, 62% gram-negative, and 19% fungal. In patients with positive isolates, the most common gram-positive organism was *Staphylococcus aureus* (20%); the most common gram-negative organisms were *Pseudomonas* species (20%) and *Escherichia coli* (16%) (Table 2).

## Factors Associated With Higher Risk of Infections

The infection rate was related to disease severity as expressed by the SAPS II score and the degree of organ failure (FIGURE). There was a relationship between the number of days spent in the ICU before the study day and the rate of infection: the infection rate increased from 32% for patients with a pre–study day ICU stay of 0 or 1 day to more than 70% for patients with a pre–study day ICU stay of more than 7 days ($P<.001$, Cochran-Armitage

**Table 1.** Basic Characteristics of Adult Patients in the EPIC II Study

| Characteristic | No. (%) All Patients (n = 13 796)[a] | Not Infected (n = 6709)[b] | Infected (n = 7087)[c] | *P* Value |
|---|---|---|---|---|
| Age, mean (95% CI), y | 60.7 (60.4-61.0) | 60.5 (60.1-60.9) | 60.9 (60.5-61.3) | .21 |
| Men | 8587 (62.3) | 4130 (61.7) | 4457 (63.0) | .12 |
| Severity score on study day, mean (95% CI)[d] | | | | |
| SAPS II | 35.1 (34.9-35.4) | 31.3 (30.9-31.6) | 38.7 (38.4-39.1) | <.001 |
| SOFA | 6.3 (6.2-6.4) | 5.2 (5.1-5.3) | 7.2 (7.1-7.3) | <.001 |
| Type of admission | | | | |
| Elective surgery | 3209 (23.3) | 2297 (34.4) | 912 (12.9) | <.001 |
| Medical | 3878 (28.2) | 1584 (23.7) | 2294 (32.4) | |
| Emergency surgery | 5298 (38.5) | 2070 (31.0) | 3228 (45.6) | |
| Trauma | 1365 (9.9) | 725 (10.9) | 640 (9.0) | |
| Reason for ICU admission | | | | |
| Respiratory | 3091 (22.4) | 845 (12.6) | 2246 (31.7) | <.001 |
| Cardiovascular | 3041 (22.0) | 1541 (23.0) | 1500 (21.2) | |
| Surveillance/monitoring | 2592 (18.8) | 1968 (29.3) | 624 (8.8) | |
| Neurologic | 2010 (14.6) | 994 (14.8) | 1016 (14.3) | |
| Digestive/liver | 1306 (9.5) | 478 (7.1) | 828 (11.7) | |
| Trauma | 1119 (8.1) | 593 (8.8) | 526 (7.4) | |
| Renal | 324 (2.3) | 119 (1.8) | 205 (2.9) | |
| Other[e] | 313 (2.3) | 171 (2.5) | 142 (2.0) | |
| Source of admission | | | | |
| Operating room/recovery | 3510 (25.7) | 2178 (32.9) | 1332 (18.9) | <.001 |
| ED/ambulance | 4010 (29.3) | 1980 (29.9) | 2030 (28.8) | |
| Hospital floor | 3789 (27.7) | 1503 (22.7) | 2286 (32.5) | |
| Other hospital | 1921 (14.1) | 751 (11.3) | 1170 (16.6) | |
| Other | 435 (3.2) | 212 (3.2) | 223 (3.2) | |
| Comorbid conditions | | | | |
| COPD | 2303 (16.7) | 872 (13.0) | 1431 (20.2) | <.001 |
| Cancer | 2086 (15.1) | 975 (14.5) | 1111 (15.7) | .06 |
| Heart failure[f] | 1342 (9.7) | 604 (9.0) | 738 (10.4) | .005 |
| Diabetes mellitus | 1336 (9.7) | 605 (9.0) | 731 (10.3) | .01 |
| Chronic renal failure | 1250 (9.1) | 494 (7.4) | 756 (10.7) | <.001 |
| Immunosuppression | 587 (4.3) | 176 (2.6) | 411 (5.8) | <.001 |
| Cirrhosis | 460 (3.3) | 195 (2.9) | 265 (3.7) | .006 |
| Hematologic cancer | 282 (2.0) | 73 (1.1) | 209 (2.9) | <.001 |
| HIV | 96 (0.7) | 18 (0.3) | 78 (1.1) | <.001 |
| No. of comorbid conditions | | | | |
| 0 | 6686 (48.5) | 3629 (54.1) | 3060 (43.2) | <.001 |
| 1 | 4434 (32.1) | 2076 (30.9) | 2358 (33.3) | |
| 2 | 1829 (13.3) | 719 (10.7) | 1110 (15.7) | |
| 3 | 626 (4.5) | 227 (3.4) | 399 (5.6) | |
| >3 | 218 (1.6) | 58 (0.9) | 160 (2.3) | |
| Treatment on admission | | | | |
| Mechanical ventilation | 7694 (56.2) | 2932 (44.1) | 4762 (67.5) | <.001 |
| Hemodialysis/hemofiltration | 1247 (9.1) | 322 (4.8) | 925 (13.1) | <.001 |

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; ED, emergency department; EPIC II, Extended Prevalence of Infection in Intensive Care; HIV, human immunodeficiency virus; ICU, intensive care unit; SAPS II, Simplified Acute Physiology Score II; SOFA, Sequential Organ Failure Assessment.
[a] Totals may not sum to 13 796, owing to missing values.
[b] Totals may not sum to 6709, owing to missing values.
[c] Totals may not sum to 7087, owing to missing values.
[d] Range of possible scores, 0-163 for SAPS II and 0-24 for SOFA.
[e] Metabolic, hematologic, obstetric/gynecologic.
[f] New York Heart Association class III-IV.

trend test) (eFigure 1). This was particularly true for infections with methicillin-resistant *Staphylococcus aureus*, *Acinetobacter* species, *Pseudomonas* species, and *Candida* species (eFigure 2).

Multivariate logistic regression analysis showed that medical admission; admission after emergency surgery or trauma; referral from the hospital floor or other hospital (with referral from the operating room as referent); presence of chronic obstructive pulmonary disease, cancer, HIV, immunosuppression, mechanical ventilation, and renal replacement therapy on the study day; and greater SAPS II scores were independently associated with a higher risk of infection (eTable 2).

### Mortality and Morbidity

Intensive care unit and hospital mortality rates were 18.2% (2370/13 011 patients) and 24.2% (3143/13 011 patients), respectively. Infected patients had higher ICU and hospital mortality rates (25.3% vs 10.7% and 33.1% vs 14.8%, respectively; $P<.001$ for both) and longer ICU and hospital lengths of stay (16 [IQR, 7-34] vs 4 [IQR, 1-14] days and 29 [IQR, 14-57] vs 13 [IQR, 7-31] days, respectively; $P<.001$ for both) than those not infected. Decisions to withhold or withdraw life-

**Table 2.** Infection Rates and Types of Organisms in Culture-Positive Infected Patients According to Geographical Region

| | No. (%)[a] | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | All | Western Europe | Eastern Europe | Central/ South America | North America | Oceania | Africa | Asia |
| No. (%) | 7087 (51.4) | 3683 (49) | 426 (56.4) | 1290 (60.3) | 607 (48.4) | 285 (48.2) | 89 (46.1) | 707 (52.6) |
| Site of infection | | | | | | | | |
| Respiratory tract | 4503 (63.5) | 2332 (63.3) | 305 (71.6)[b] | 851 (66) | 345 (56.8)[b] | 165 (57.9) | 41 (46.1)[b] | 464 (65.6) |
| Abdominal | 1392 (19.6) | 778 (21.1) | 93 (21.8) | 228 (17.7)[b] | 101 (16.6) | 50 (17.5) | 16 (18) | 126 (17.8) |
| Bloodstream | 1071 (15.1) | 546 (14.8) | 53 (12.4) | 139 (10.8)[b] | 157 (25.9)[b] | 49 (17.2) | 16 (18) | 111 (15.7) |
| Renal/urinary tract | 1011 (14.3) | 411 (11.2) | 84 (19.7)[b] | 222 (17.2)[b] | 135 (22.2)[b] | 33 (11.6) | 15 (16.9) | 111 (15.7)[b] |
| Skin | 467 (6.6) | 242 (6.6) | 37 (8.7) | 73 (5.7) | 26 (4.3) | 30 (10.5) | 8 (9.0) | 51 (7.2) |
| Catheter-related | 332 (4.7) | 171 (4.6) | 21 (4.9) | 73 (5.7) | 16 (2.6) | 15 (5.3) | 4 (4.5) | 32 (4.5) |
| CNS | 208 (2.9) | 100 (2.7) | 20 (4.7) | 40 (3.1) | 14 (2.3) | 11 (3.9) | 4 (4.5) | 19 (2.7) |
| Others | 540 (7.6) | 289 (7.8) | 31 (7.3) | 87 (6.7) | 62 (10.2) | 22 (7.7) | 14 (15.7)[b] | 35 (5.0)[b] |
| Microorganisms | | | | | | | | |
| Positive isolates | 4947 (69.8) | 2678 (72.7) | 357 (83.8)[b] | 719 (55.7)[b] | 457 (75.3) | 204 (71.6) | 54 (60.7) | 478 (67.6)[b] |
| Gram-positive | 2315 (46.8) | 1311 (49.0) | 185 (51.8) | 273 (38.0)[b] | 252 (55.1) | 104 (51.0) | 27 (50.0) | 163 (34.1)[b] |
| *Staphylococcus aureus* | 1012 (20.5) | 525 (19.6) | 77 (21.6) | 138 (19.2) | 123 (26.9)[b] | 56 (27.5)[b] | 16 (29.6) | 77 (16.1) |
| MRSA | 507 (10.2) | 233 (8.7) | 37 (10.4) | 79 (11.0) | 80 (17.5)[b] | 19 (9.3) | 11 (20.4)[b] | 48 (10.0) |
| *S epidermidis* | 535 (10.8) | 301 (11.2) | 43 (12) | 67 (9.3) | 56 (12.3) | 17 (8.3) | 8 (14.8) | 43 (9.0) |
| *Streptococcus pneumoniae* | 203 (4.1) | 127 (4.7) | 16 (4.5) | 24 (3.3) | 20 (4.4) | 5 (2.5) | 3 (5.6) | 8 (1.7)[b] |
| VSE | 352 (7.1) | 250 (9.3) | 35 (9.8) | 17 (2.4)[b] | 24 (5.3)[b] | 9 (4.4) | 0[b] | 17 (3.6)[b] |
| VRE | 186 (3.8) | 113 (4.2) | 16 (4.5) | 15 (2.1)[b] | 22 (4.8) | 10 (4.9) | 0 | 10 (2.1) |
| Other | 319 (6.4) | 184 (6.9) | 15 (4.2) | 29 (4.0)[b] | 48 (10.5) | 19 (9.3) | 4 (7.4) | 20 (4.2) |
| Gram-negative | 3077 (62.2) | 1573 (58.7) | 258 (72.3)[b] | 510 (70.9)[b] | 228 (49.9)[b] | 122 (59.8) | 31 (57.4) | 355 (74.3)[b] |
| *Escherichia coli* | 792 (16.0) | 458 (17.1) | 53 (14.8) | 103 (14.3) | 65 (14.2) | 27 (13.2) | 6 (11.1) | 80 (16.7) |
| *Enterobacter* | 345 (7.0) | 184 (6.9) | 29 (8.1) | 62 (8.6) | 37 (8.1) | 7 (3.4) | 4 (7.4) | 22 (4.6) |
| *Klebsiella* species | 627 (12.7) | 261 (9.7) | 76 (21.3)[b] | 116 (16.1)[b] | 41 (9) | 24 (11.8) | 10 (18.5) | 99 (20.7)[b] |
| *Pseudomonas* species | 984 (19.9) | 458 (17.1) | 103 (28.9)[b] | 189 (26.3)[b] | 59 (12.9) | 30 (14.7) | 8 (14.8) | 137 (28.7)[b] |
| *Acinetobacter* species | 435 (8.8) | 149 (5.6) | 61 (17.1)[b] | 99 (13.8)[b] | 17 (3.7) | 9 (4.4) | 8 (14.8)[b] | 92 (19.2)[b] |
| Other | 840 (17.0) | 487 (18.2) | 54 (15.1) | 121 (16.8) | 52 (11.4)[b] | 42 (20.6) | 11 (20.4) | 73 (15.3) |
| ESBL-producing | 93 (1.9) | 47 (1.8) | 7 (2.0) | 21 (2.9) | 1 (0.2)[b] | 0 | 1 (1.9) | 16 (3.3) |
| Anaerobes | 222 (4.5) | 142 (5.3) | 12 (3.4) | 10 (1.4)[b] | 36 (7.9) | 7 (3.4) | 1 (1.9) | 14 (2.9) |
| Other bacteria | 76 (1.5) | 33 (1.2) | 7 (2.0) | 14 (1.9) | 4 (0.9) | 4 (2.0) | 3 (5.6) | 11 (2.3) |
| Fungi | | | | | | | | |
| *Candida* | 843 (17) | 495 (18.5) | 66 (18.5) | 92 (12.8)[b] | 83 (18.2) | 26 (12.7) | 6 (11.1) | 75 (15.7) |
| *Aspergillus* | 70 (1.4) | 44 (1.6) | 1 (0.3) | 5 (0.7) | 12 (2.6) | 3 (1.5) | 0 | 5 (1) |
| Other | 50 (1) | 22 (0.8) | 5 (1.4) | 7 (1) | 10 (2.2) | 2 (1) | 0 | 4 (0.8) |
| Parasites | 34 (0.7) | 18 (0.7) | 2 (0.6) | 6 (0.8) | 3 (0.7) | 2 (1) | 0 | 3 (0.6) |
| Other organisms | 192 (3.9) | 122 (4.6) | 9 (2.5) | 15 (2.1)[b] | 22 (4.8) | 8 (3.9) | 2 (3.7) | 14 (2.9) |

Abbreviations: CNS, central nervous system; ESBL, extended-spectrum β-lactamases; MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant *Enterococcus;* VSE, vancomycin-sensitive *Enterococcus.*

[a] Percentages do not necessarily equal 100, because patients may have had more than 1 type of infection or microorganism.

[b] Significant at 5% (with Bonferroni correction) vs Western Europe.

sustaining measures were made in 1232 patients (8.9%) and were more common in infected than in noninfected patients (890/3256 [27.3%] vs 342/2442 [14.0%], $P<.001$).

In a multivariate analysis of all patients, with hospital mortality as the dependent variable and adjusting for possible confounders, infection was independently associated with a greater risk of hospital mortality (33.1% vs 14.8%; adjusted odds ratio, 1.51; 95% confidence interval, 1.36-1.68; $P<.001$). Other factors associated independently with a greater risk of in-hospital death are shown in TABLE 3. In patients with infections, factors independently associated with a greater risk of hospital death were comorbid cancer, heart failure, immunosuppression, or cirrhosis; infection with *Pseudomonas, Enterococcus,* or *Acinetobacter* species; older age; greater disease severity; and treatment with mechanical ventilation or renal replacement therapy on the day of the study (eTable 3).

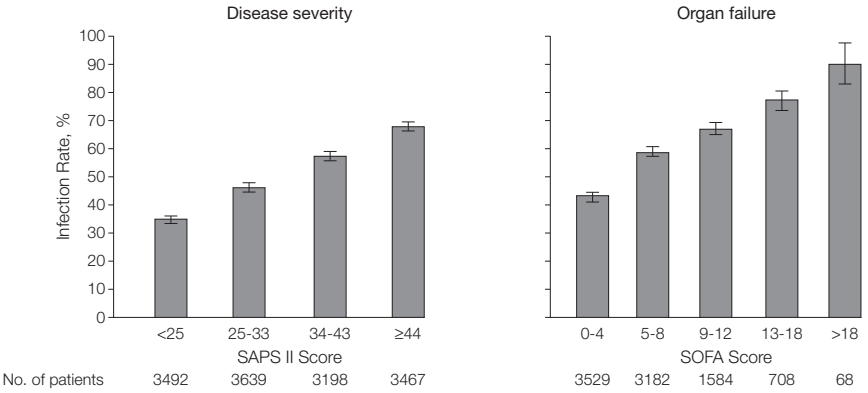
### International Comparisons

Central and South America had the highest infection rate (60%) and Africa had the lowest (46%) (Table 2). There was considerable variation in the types of organisms isolated from the different geographical regions; rates of infection with *Acinetobacter* differed most markedly, ranging from 3.7% in North America to 19.2% in Asia (Table 2). Infection rates were related to health care expenditure, with higher rates of infection reported in countries that had a lower proportion of gross domestic product devoted to health care (61.9% infection rate in countries devoting <5% of gross domestic product to health; 53.8% in those devoting 5%-9%; 48.0% in those devoting >9%; $P<.001$ by Cochran-Armitage trend test). Intensive care unit and hospital mortality rates were highest in ICUs from Central and South America and Eastern Europe and lowest in ICUs from Oceania (eTable 4). There was a significant relationship between the percentage of infected patients and hospital mortality rate (eFigure 3).

## COMMENT

The data from this large international collaboration highlight the common occurrence of infections in contemporary ICUs, with 46% to 60% of ICU patients classified by the attending physician as infected on the day of the study. Infected patients had more co-

**Figure.** Relationship Between Rate of Infection and Disease Severity and Organ Failure




$P<.001$ for both panels, by Cochran-Armitage trend test. Range of possible scores is 0-163 for SAPS II (Simplified Acute Physiology Score II) and 0-24 for SOFA (Sequential Organ Failure Asessment). Error bars indicate 95% confidence intervals.

**Table 3.** Multivariable Logistic Regression Analysis With Hospital Mortality as the Dependent Variable

| Variable | OR (95% CI)[a] | *P* Value |
|---|---|---|
| Type of admission | | |
| Elective surgery | 1 [Reference] | |
| Medical | 1.18 (0.99-1.41) | .06 |
| Emergency surgery | 1.56 (1.34-1.82) | <.001 |
| Trauma | 1.34 (1.06-1.70) | .01 |
| Source of admission | | |
| Operating room/recovery | 1 [Reference] | |
| ED/ambulance | 0.94 (0.80-1.11) | .47 |
| Hospital floor | 1.37 (1.18-1.59) | <.001 |
| Other hospital | 1.01 (0.85-1.21) | .91 |
| Other | 1.14 (0.85-1.53) | .39 |
| Comorbid conditions | | |
| COPD | 1.21 (1.07-1.38) | <.01 |
| Cancer | 1.33 (1.15-1.53) | <.001 |
| Heart failure[b] | 1.45 (1.25-1.70) | <.001 |
| Diabetes mellitus | 0.98 (0.83-1.15) | .79 |
| Chronic renal failure | 1.02 (0.87-1.20) | .81 |
| Immunosuppression | 1.83 (1.47-2.28) | <.001 |
| Cirrhosis | 2.14 (1.68-2.74) | <.001 |
| Hematologic cancer | 1.05 (0.76-1.45) | .75 |
| HIV | 0.90 (0.53-1.52) | .69 |
| Age, per year | 1.01 (1.01-1.01) | <.001 |
| Male sex | 0.99 (0.89-1.09) | .82 |
| Mechanical ventilation | 1.90 (1.70-2.13) | <.001 |
| Hemodialysis/hemofiltration | 1.58 (1.35-1.85) | <.001 |
| SAPS II score, per point | 1.06 (1.05-1.06) | <.001 |
| Infection | 1.51 (1.36-1.68) | <.001 |

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; ED, emergency department; HIV, human immunodeficiency virus; OR, odds ratio; SAPS II, Simplified Acute Physiology Score II.
[a] Adjusted for hospital and organizational factors and for geographical region.
[b] New York Heart Association class III-IV.

morbid conditions and higher SAPS II scores on admission.

As in other recent epidemiologic studies,[2-4,9,12,18-23] the most common focus of infection in patients in our study was the lung, followed by the abdomen and bloodstream. Although studies have suggested an increasing incidence of gram-positive organisms[24] and the Sepsis Occurrence in Acutely Ill Patients (SOAP) study reported an equal frequency of gram-positive and gram-negative organisms,[2] in the present study gram-negative organisms were more commonly isolated than gram-positive organisms. Patterns of infecting organisms were similar to those in previous studies, with predominant organisms being *S aureus* (the most commonly isolated organism, despite the overall predominance of gram-negative organisms), *Pseudomonas* species, *Enterobacteriaceae* (mainly *E coli*), and fungi.[2] Interestingly, *Acinetobacter* was involved in 9% of all infections, similar to the rate reported in the first EPIC study[25] but considerably higher than the 3.6% reported in the more recent SOAP study.[2]

There were significant regional differences in the organisms isolated from microbiological cultures, with a particularly striking variation in the prevalence of *Acinetobacter*. Importantly, local infection control measures may alter infection rates, particularly with *Acinetobacter*, because it is present in the water supply of many hospitals, and simple infection control measures such as not flushing nasogastric tubes with tap water and separating clean from dirty ventilator circuits can influence infection rates.[26,27] That differences exist in rates of *Acinetobacter* infection from one country to the next suggests an opportunity for preventive control measures directed at the ICU environment. Moreover, this finding also emphasizes the importance of using local data to guide empirical antibiotic therapy.[28] In multivariate analysis, infection with *Acinetobacter* was associated with an increased risk of hospital death. Given the high level of resistance of *Acinetobacter* to many antibiotics, including carbapenems, and the high associated mortality,[29] this pathogen presents a continuing challenge in today's ICU. Infections with *Pseudomonas* species were also associated with an increased risk of in-hospital death, as has been reported in the SOAP study.[2]

EPIC II was conducted 15 years after the original EPIC study,[14] which was limited to Western Europe and included slightly more than 10 000 patients. In contrast to the EPIC study, in EPIC II we did not focus our analysis on nosocomial infections, because we were concerned that it may be difficult to distinguish between community-acquired, hospital-acquired, and ICU-acquired infections. As in the EPIC study[14] and more recently the SOAP study,[2] there was a relationship between the prevalence of infection and mortality for the various countries. Importantly, this relationship was present overall but also for countries of Western Europe, which represent a more homogeneous region and contributed most patients to this study. We also noted a significant relationship between the time spent in the ICU prior to the study day and the development of infection, particularly for infections due to methicillin-resistant *Staphylococcus aureus*, *Acinetobacter, Pseudomonas* species, and *Candida* species.

The study also revealed important differences in outcomes in various parts of the world. For example, mortality rates were lower in Oceania, both overall and in infected patients, than in other regions. The reasons for this are not entirely clear, although differences in patient characteristics are likely to be at least in part responsible. It is also possible that lead-time bias may play a role, because patients may be admitted to the ICU earlier in some regions than in others. The huge variability in critical care services among North American and European countries, with wide differences both in numbers of beds and in volumes of admissions, has also been recently highlighted[30] and is likely responsible for some of the regional differences in our data.

Interestingly, the rate of infection was related to the proportion of gross domestic product allocated to health care expenses, because countries with lower health care expenditures had higher rates of infection. It would have been interesting to further explore this relationship, perhaps considering also the percentage of gross domestic product allocated specifically to ICU spending rather than to health care in general, but we were unable to locate these data for all countries. Clearly, multiple factors can influence the relationship between health care spending and infection rates, including national antibiotic availability and policy, infection control practices, vaccine availability and use, and public health strategies and educational programs to prevent infection, which we were not able to control for in this study. There are few data available on this topic. One recent article,[30] although reporting only a weak correlation between ICU beds per 100 000 population and health care spending per capita in 8 countries, did note an inverse correlation between the provision of ICU beds and the frequency of sepsis and hospital mortality using data from 2 large independent sources, the SOAP study[2] and the SAPS 3 database.[31]

Our study has advantages and limitations. An obvious strength is the international nature of the study, which collected data on patterns of infection in a large and diverse group of patients across all geographic boundaries. However, comparisons among geographic regions should be interpreted with caution, because clearly there are large differences in health care systems, ICU facilities, and regional policies for infectious disease management. Nevertheless, such a worldwide study has the advantage that the apparent differences in practice patterns can be used to probe independent influences of patient and management factors on epidemiology and outcome. To avoid any possibility of industry influence, the study was not funded. The size of this collaboration stresses the importance of the topic and the desire to contribute to international projects without financial incentive.

However, the voluntary nature of the study can be a potential source of bias. Moreover, the high proportion of university hospitals may have led to a patient case-mix that is not representative

of all ICUs. Another disadvantage is that there was no data monitoring, and results relied on the correct interpretation and use of the various definitions provided. A prevalence study has the advantage of requiring a relatively limited data set while including a large number of patients; however, prevalence studies can overestimate the number of patients with diseases of long duration, such as sepsis. Lastly, although the study date was chosen to minimize seasonal effects as much as possible, there is no way to be completely sure that such effects did not influence the results.

## CONCLUSIONS

The EPIC II study demonstrates that infections remain a common problem in ICU patients. There is a strong relation between presence of infection and length of ICU stay and mortality as well as a significant inverse relation between the prevalence of infections and extent of government health care expenditure. Major international differences exist in the prevalence of infections, types of infecting microorganisms, and mortality rates. These important data provide a picture of patterns of infection around the world, which can enhance understanding of global and regional differences and provide pointers to help optimize infection prophylaxis and management.

**Author Affiliations:** Department of Intensive Care, Erasme Hospital, Université libre de Bruxelles, Brussels, Belgium (Dr Vincent); Critical Care Department, Joan XXIII University Hospital, CIBERes, URV-IISPV Tarragona, Spain (Dr Rello); Department of Surgery, Interdepartmental Division of Critical Care Medicine, University of Toronto, St Michael's Hospital, Toronto, Ontario, Canada (Dr Marshall); Department of Intensive Care, Hospital Israelita Albert Einstein, São Paulo, Brazil (Dr Silva); Department of Pulmonary/Critical Care, University of Texas Health Science Center, San Antonio (Dr Anzueto); Department of Anesthesiology and Intensive Care, Hôpital Nord, Marseille, France (Dr Martin); Department of Intensive Care, Hospital de St António dos Capuchos, Centro Hospitalar de Lisboa Central, E.P.E., Lisbon, Portugal (Dr Moreno); Burns, Trauma and Critical Care Research Centre, University of Queensland, Brisbane, Queensland, Australia (Dr Lipman); Department of Anesthesia and Intensive Care, The Chinese University of Hong Kong, and Prince of Wales Hospital, Shatin, Hong Kong, China (Dr Gomersall); and Department of Anesthesiology and Intensive Care, Friedrich-Schiller University, Jena, Germany (Drs Sakr and Reinhart).

**Author Contributions:** Dr Vincent had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
*Study concept and design:* Vincent, Rello, Marshall, Silva, Anzueto, Martin, Moreno, Lipman, Gomersall, Sakr, Reinhart.
*Acquisition of data:* Vincent, Rello, Marshall, Silva, Anzueto, Martin, Moreno, Lipman, Gomersall, Sakr, Reinhart.
*Analysis and interpretation of data:* Vincent, Rello, Marshall, Silva, Anzueto, Martin, Moreno, Lipman, Gomersall, Sakr, Reinhart.
*Drafting of the manuscript:* Vincent.
*Critical revision of the manuscript for important intellectual content:* Vincent, Rello, Marshall, Silva, Anzueto, Martin, Moreno, Lipman, Gomersall, Sakr, Reinhart.
*Statistical analysis:* Vincent, Sakr.
*Administrative, technical or material support:* Vincent.
*Study supervision:* Vincent.
**Financial Disclosures:** None reported.
**Additional Information:** The eAppendix, eTables 1 through 4, and eFigures 1 through 3 are available at http://www.jama.com.
**Additional Contributions:** We thank Hassane Njimi, MSc, PhD, Department of Intensive Care, Erasme University Hospital, Brussels, Belgium, for his help with the data management and statistical analyses. Dr Njimi received no extra compensation for his contributions.

### REFERENCES

**1.** Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Crit Care Med*. 2001;29(7):1303-1310.
**2.** Vincent JL, Sakr Y, Sprung CL, et al; Sepsis Occurrence in Acutely Ill Patients Investigators. Sepsis in European intensive care units: results of the SOAP study. *Crit Care Med*. 2006;34(2):344-353.
**3.** Harrison DA, Welch CA, Eddleston JM. The epidemiology of severe sepsis in England, Wales and Northern Ireland, 1996 to 2004: secondary analysis of a high quality clinical database, the ICNARC Case Mix Programme Database. *Crit Care*. 2006;10(2):R42.
**4.** Esteban A, Frutos-Vivar F, Ferguson ND, et al. Sepsis incidence and outcome: contrasting the intensive care unit with the hospital ward. *Crit Care Med*. 2007; 35(5):1284-1289.
**5.** Vincent JL, Abraham E, Annane D, Bernard G, Rivers E, Van den Berghe G. Reducing mortality in sepsis: new directions. *Crit Care*. 2002;6(suppl 3):S1-S18.
**6.** Martin GS, Mannino DM, Eaton S, Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. *N Engl J Med*. 2003;348(16):1546-1554.
**7.** Padkin A, Goldfrad C, Brady AR, Young D, Black N, Rowan K. Epidemiology of severe sepsis occurring in the first 24 hrs in intensive care units in England, Wales, and Northern Ireland. *Crit Care Med*. 2003; 31(9):2332-2338.
**8.** Weycker D, Akhras KS, Edelsberg J, Angus DC, Oster G. Long-term mortality and medical care charges in patients with severe sepsis. *Crit Care Med*. 2003; 31(9):2316-2323.
**9.** Brun-Buisson C, Meshaka P, Pinton P, Vallet B; EPISEPSIS Study Group. EPISEPSIS: a reappraisal of the epidemiology and outcome of severe sepsis in French intensive care units. *Intensive Care Med*. 2004;30(4):580-588.
**10.** Finfer S, Bellomo R, Lipman J, French C, Dobb G, Myburgh J. Adult-population incidence of severe sepsis in Australian and New Zealand intensive care units. *Intensive Care Med*. 2004;30(4):589-596.
**11.** Moreno RP, Metnitz B, Adler L, Hoechtl A, Bauer P, Metnitz PG; SAPS 3 Investigators. Sepsis mortality prediction based on predisposition, infection and response. *Intensive Care Med*. 2008;34(3):496-504.
**12.** Silva E, Pedro MA, Sogayar AC, et al; Brazilian Sepsis Epidemiological Study. Brazilian Sepsis Epidemiological Study (BASES study). *Crit Care*. 2004; 8(4):R251-R260.
**13.** Cheng B, Xie G, Yao S, et al. Epidemiology of severe sepsis in critically ill surgical patients in ten university hospitals in China. *Crit Care Med*. 2007; 35(11):2538-2546.
**14.** Vincent JL, Bihari D, Suter PM, et al; EPIC International Advisory Committee. The prevalence of nosocomial infection in intensive care units in Europe: results of the European Prevalence of Infection in Intensive Care (EPIC) study. *JAMA*. 1995;274(8):639-644.
**15.** Le Gall J-R, Lemeshow S, Saulnier F. A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. *JAMA*. 1993;270(24):2957-2963.
**16.** Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. *Intensive Care Med*. 1996;22(7):707-710.
**17.** Calandra T, Cohen J; International Sepsis Forum Definition of Infection in the ICU Consensus Conference. The International Sepsis Forum consensus conference on definitions of infection in the intensive care unit. *Crit Care Med*. 2005;33(7):1538-1548.
**18.** van Gestel A, Bakker J, Veraart CP, van Hout BA. Prevalence and incidence of severe sepsis in Dutch intensive care units. *Crit Care*. 2004;8(4):R153-R162.
**19.** Záhorec R, Firment J, Straková J, et al. Epidemiology of severe sepsis in intensive care units in the Slovak Republic. *Infection*. 2005;33(3):122-128.
**20.** Engel C, Brunkhorst FM, Bone HG, et al. Epidemiology of sepsis in Germany: results from a national prospective multicenter study. *Intensive Care Med*. 2007;33(4):606-618.
**21.** Karlsson S, Varpula M, Ruokonen E, et al. Incidence, treatment, and outcome of severe sepsis in ICU-treated adults in Finland: the Finnsepsis study. *Intensive Care Med*. 2007;33(3):435-443.
**22.** Sundararajan V, Macisaac CM, Presneill JJ, Cade JF, Visvanathan K. Epidemiology of sepsis in Victoria, Australia. *Crit Care Med*. 2005;33(1):71-80.
**23.** Martin CM, Priestap F, Fisher H, et al; STAR Registry Investigators. A prospective, observational registry of patients with severe sepsis: the Canadian Sepsis Treatment and Response Registry. *Crit Care Med*. 2009;37(1):81-88.
**24.** Friedman G, Silva E, Vincent JL. Has the mortality of septic shock changed with time? *Crit Care Med*. 1998;26(12):2078-2086.
**25.** Spencer RC. Predominant pathogens found in the European Prevalence of Infection in Intensive Care study. *Eur J Clin Microbiol Infect Dis*. 1996;15 (4):281-285.
**26.** Hartstein AI, Rashad AL, Liebler JM, et al. Multiple intensive care unit outbreak of *Acinetobacter calcoaceticus* subspecies *anitratus* respiratory infection and colonization associated with contaminated, reusable ventilator circuits and resuscitation bags. *Am J Med*. 1988;85(5):624-631.
**27.** Barchitta M, Cipresso R, Giaquinta L, et al. Acquisition and spread of *Acinetobacter baumannii* and *Stenotrophomonas maltophilia* in intensive care patients. *Int J Hyg Environ Health*. 2009;212(3): 330-337.
**28.** Beardsley JR, Williamson JC, Johnson JW, Ohl CA, Karchmer TB, Bowton DL. Using local microbiologic data to develop institution-specific guidelines for the treatment of hospital-acquired pneumonia. *Chest*. 2006;130(3):787-793.
**29.** Falagas ME, Rafailidis PI. Attributable mortality of *Acinetobacter baumannii*: no longer a controversial issue. *Crit Care*. 2007;11(3):134.
**30.** Wunsch H, Angus DC, Harrison DA, et al. Variation in critical care services across North America and Western Europe. *Crit Care Med*. 2008;36(10): 2787-2793, e1-e9.
**31.** Metnitz PG, Moreno RP, Almeida E, et al; SAPS 3 Investigators. SAPS 3—from evaluation of the patient to evaluation of the intensive care unit, I: objectives, methods and cohort description. *Intensive Care Med*. 2005;31(10):1336-1344.

# Antibiotic Usage and Resistance

## Gaining or Losing Ground on Infections in Critically Ill Patients?

Steven M. Opal, MD

Thierry Calandra, MD, PhD

In this issue of *JAMA*, Vincent and colleagues[1] report the results of a remarkable point prevalence survey of infections in intensive care units (ICUs) worldwide and the association of these infections with outcomes of critically ill patients. The study included 13 796 patients present on a single day (May 8, 2007) in more than 1200 ICUs from 75 countries around the world. Known as EPIC II (Extended Prevalence of Infection in the ICU), the study is a 15-year follow-up to another point prevalence investigation, EPIC (European Prevalence of Infection in the ICU),[2] which was conducted in 1995 and included 10 038 patients, primarily from ICUs in western Europe; many of the same European institutions participated in both studies. The scope and magnitude of EPIC II, the largest of any ICU infection prevalence study, reveals several noteworthy insights into the current practice patterns of antibiotic use and infection risks in ICU patients.

The burden of infection among critically ill patients is striking, especially given the marked efforts in recent years to decrease ICU infections. For instance, in EPIC II, 51% of ICU patients were considered infected and 71% were receiving antimicrobial agents on the study day, with some antibiotic exposure for prophylaxis, and the majority of patients were receiving 2 or more antibiotics.[1] In the 1995 EPIC study, 44.8% of ICU patients were considered infected and 62.3% were receiving antimicrobial agents. In EPIC II, the risk of infection increased with disease severity and length of ICU stay,[1] infection was independently associated with hospital mortality, and infection with multidrug-resistant organisms such as *Acinetobacter* and *Pseudomonas* species and fungal pathogens was statistically correlated with excess mortality rates.[1]

Some concerning trends are evident when comparing the microbiology data from 15 years ago with those from the present study. Gram-negative bacterial infections, previously thought to be on the wane,[3] now outnumber gram-positive infections in ICU patients, accounting for 63% of infections in 2007 vs 39.1% of infections in 1995. This is not a favorable trend, because resistance among gram-negative bacteria is increasing[4,5] and the number of therapeutic alternatives to treat these infections is diminishing.[6] The developmental pipeline for new classes of antimicrobial agents against gram-negative bacteria has virtually run dry, and the prospects for new drugs against these pathogens in the immediate future are not good.

The proportion of ICU infections caused by *Staphylococcus aureus* decreased from 30.1% in EPIC to 20.5% in EPIC II, and prevalence of methicillin resistance among these isolates decreased from 60% to 50%.[7] However, resistance trends are regional. The majority of *S aureus* isolates from North America were resistant to methicillin,[1] and *S aureus* is still the single most commonly recognized microbial pathogen accounting for ICU infection. Fungal infections increased (from a prevalence of 17% in 1995 to 19% in 2007), although severe viral infections in ICU patients have remained relatively rare (<1%).[1,2] This situation will likely change radically over the next year as pandemic 2009 influenza A(H1N1) continues to cause critical illness worldwide.[8]

Bacterial pathogens have a seemingly unlimited capacity to develop resistance to environmental toxins such as antimicrobial agents.[9] Evolutionary forces have outfitted bacteria with sufficient genetic variability and mechanisms for genetic exchange to rapidly defend themselves against antimicrobial agents. The widespread use of multiple classes of antibiotics within the ICU setting makes critical care areas the epicenter for the acquisition and dissemination of antibiotic resistance in bacterial pathogens. Selection pressures created by intense antibiotic exposure favor the selection and expression of antibiotic resistance genes among bacterial populations. Pathogens with the capacity to express and exchange these resistance genes flourish in environments with heavy antibiotic use.

The prevalence of intrinsically multidrug-resistant, environmental bacteria (eg, *Pseudomonas, Acinetobacter, Stenotrophomonas* species) has continued to be substantial in ICU patients, with these species combined accounting for a substantial proportion of gram-negative infections in both

**See also p 2323.**

**Author Affiliations:** Infectious Disease Division, Warren Alpert Medical School of Brown University, Providence, Rhode Island (Dr Opal); and Infectious Disease Service, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland, and University of Lausanne, Lausanne (Dr Calandra).
**Corresponding Author:** Steven M. Opal, MD, Infectious Disease Division, Memorial Hospital of Rhode Island, 111 Brewster St, Pawtucket, RI 02806 (steven_opal@brown.edu).

studies. Moreover, among commensal microorganisms, those with antibiotic resistance genes, such as enterococci and enteric gram-negative bacteria, are selected for over their antibiotic-susceptible counterparts in an ICU setting. Resistance genes are often located on gene cassettes known as integrons that can be mobilized by transposable elements and spread by multiresistant R plasmids to other bacterial pathogens.[9] Dissemination of antibiotic-resistant bacteria within the ICU environment is an ongoing risk. Vulnerable patients with multiple catheters and instruments and with various degrees of immune dysregulation from medications and underlying disease processes are at risk for colonization and infection by antibiotic-resistant bacteria.

The critical care clinician faces a therapeutic dilemma on a daily basis. Despite published guidelines,[10] the uncertain interaction at the host-pathogen interface makes it difficult to distinguish between colonization vs early infection in the ICU patient. Early intervention with appropriate antibiotics is lifesaving in patients with severe infection, yet the profligate use of antimicrobial agents contributes to progressive antimicrobial resistance.[11] Quality-of-care indicators now penalize physicians for delayed antibiotic use in specific situations; no such imperatives are used to limit extended and unnecessary antibiotic use. With few alternatives available, it is understandable why intensivists opt for liberal antibiotic use and rely heavily on these therapeutic agents to carry patients through critical illness to recovery.

In light of the current therapeutic quandary that ICU clinicians face, what does the future hold for antimicrobial therapy and emerging antibiotic resistance? The increasing prevalence of antibiotic resistance genes among bacteria in the community and the continued exposure of commensal bacteria to antibiotics ensures that antibiotic resistance will persist and likely worsen in the future. While contamination from the environment and cross-infection from the hands and devices of health care workers account for some infections, many infections are caused by the intrinsic microorganisms residing within or on the patient at the time of arrival in the ICU. Critically ill patients regularly exposed to invasive procedures will continue to experience morbidity from bacterial and fungal infections. Without some radical new intervention (such as antibacterial vaccines, biotherapy, immunotherapy, or genome-based therapies), trends in antibiotic resistance will continue to emerge, and therapeutic options will become increasingly limited.

With few new antibiotic classes in development, the functional antibacterial activity of existing antimicrobial agents must be preserved. Use of infection control measures that prevent cross-contamination from other patients or the ICU environment is a primary safety issue, but these measures will not eliminate the risk of infection or antibiotic resistance.[6] Good antimicrobial stewardship using pharmacokinetic or pharmacodynamic principles to optimize the benefit and minimize the risk of antibiotics should be the norm in ICU patients.[11] Limiting use of antibiotics to patients with clear evidence of infection rather than colonization is essential, and discontinuation of antibiotics when their possible benefits have been obtained is also critical. New initiatives such as the use of biomarkers to aid clinicians in the decision to discontinue unnecessary antibiotic therapy should be encouraged.[12] Immunotherapies and reduced reliance on invasive diagnostic and hemodynamic monitoring techniques might also be useful in the future. Development of novel classes of antimicrobial agents is sadly lacking and needs to be a major research priority.[6] New drugs are needed to replace the increasingly obsolete classes of antibiotics that currently exist. A "postantibiotic era" is difficult to contemplate but might become a reality unless the threat of progressive antibiotic resistance is taken seriously.

**Financial Disclosures:** None reported.

**REFERENCES**

**1.** Vincent J-L, Rello J, Marshall J, et al; for the EPIC II Group of Investigators. International study of the prevalence and outcomes of infection in intensive care units. *JAMA*. 2009;302(21):2323-2329.
**2.** Vincent J-L, Bihari D, Suter PM, et al; EPIC International Advisory Committee. The prevalence of nosocomial infection in intensive care units in Europe: results of the European Prevalence of Infection in Intensive Care (EPIC Study). *JAMA*. 1995; 274(8):639-644.
**3.** Martin GS, Mannino DM, Eaton S, Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. *N Engl J Med*. 2003;348(16):1546-1554.
**4.** Paterson DL, Doi Y. A step closer to extreme drug resistance (XDR) in gram-negative bacilli. *Clin Infect Dis*. 2007;45(9):1179-1181.
**5.** Barchitta M, Cipresso R, Giaquinta L, et al. Acquisition and spread of *Acinetobacter baumannii* and *Stenotrophomonas maltophilia* in intensive care patients. *Int J Hyg Environ Health*. 2009;212(3):330-337.
**6.** Talbot GH, Bradley J, Edwards JE Jr, Gilbert D, Scheld M, Bartlett JG; Antimicrobial Availability Task Force of the Infectious Diseases Society of America. Bad bugs need drugs: an update on the development pipeline from the Antimicrobial Availability Task Force of the Infectious Diseases Society of America. *Clin Infect Dis*. 2006;42(5):657-668.
**7.** Spencer RC. Predominant pathogens found in the European Prevalence of Infection in Intensive Care Study. *Eur J Clin Microbiol Infect Dis*. 1996;15(4): 281-285.
**8.** Kumar A, Zarychanski R, Pinto R, et al. Critically ill patients with 2009 influenza A(H1N1) infection in Canada [published online ahead of print October 12, 2009]. *JAMA*. 2009;302(17):1872-1879.
**9.** Opal SM, Pop-Vicas A. Molecular mechanisms of antibiotic resistance in bacteria. In: Mandell GL, Bennett JE, Dolin R, eds. *Mandell, Douglas and Bennett's Principles and Practice of Infectious Diseases.* 7th ed. Philadelphia, PA: Elsevier; 2009: 279-296.
**10.** Calandra T, Cohen J; International Sepsis Forum Definition of Infection in the ICU Consensus Conference. The International Sepsis Forum Concensus Conference on Definitions of Infection in the Intensive Care Unit. *Crit Care Med*. 2005; 33(7):1538-1548.
**11.** Mandell LA, Wunderink RG, Anzueto A, et al; Infectious Diseases Society of America; American Thoracic Society. Infectious Diseases Society of America /American Thoracic Society Consensus Guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis*. 2007;44(suppl 2): S27-S72.
**12.** Schuetz P, Christ-Crain M, Thomann R, et al; ProHOSP Study Group. Effect of procalcitonin-based guidelines vs standard guidelines on antibiotic use for lower respiratory tract infections. *JAMA*. 2009;302(10):1059-1066.