Nosocomial infections (NIs) now concern 5 to 15% of hospitalized patients and can lead to complications in 25 to 33% of those patients admitted to ICUs. The most common causes are pneumonia related to mechanical ventilation, intra-abdominal infections following trauma or surgery, and bacteremia derived from intravascular devices. This overview is targeted at ICU physicians to convince them that the principles of infection control in the ICU are based on simple concepts and that the application of preventive strategies should not be viewed as an administrative or constraining control of their activity but, rather, as basic measures that are easy to implement at the bedside. A detailed knowledge of the epidemiology, based on adequate surveillance methodologies, is necessary to understand the pathophysiology and the rationale of preventive strategies that have been demonstrated to be effective. The principles of general preventive measures such as the implementation of standard and isolation precautions, and the control of antibiotic use are reviewed. Specific practical measures, targeted at the practical prevention and control of ventilator-associated pneumonia, sinusitis, and bloodstream, urinary tract, and surgical site infections are detailed. Recent data strongly confirm that these strategies may only be effective over prolonged periods if they can be integrated into the behavior of all staff members who are involved in patient care. Accordingly, infection control measures are to be viewed as a priority and have to be integrated fully into the continuous process of improvement of the quality of care.

Key words: bloodstream infection; critical care; epidemiology; nosocomial infection; prevention; ventilator-associated pneumonia

Abbreviations: APACHE = acute physiology and chronic health evaluation; CDC = Centers for Disease Control and Prevention; CFU = colony-forming units; CI = confidence interval; CoNS = coagulase-negative staphylococci; CVC = central venous catheter; ESBL = extended-spectrum β-lactamase; HCW = health-care worker; HICPAC = Healthcare Infection Control Practices Advisory Committee; MIC50 = minimum inhibitory concentration; MRSA = methicillin-resistant Staphylococcus aureus; NI = nosocomial infection; NNIS = National Nosocomial Infection Surveillance system; OR = odds ratio; RR = relative risk; SDD = selective digestive decontamination; SSI = surgical site infection; UTI = urinary tract infection; VRE = vancomycin-resistant enterococci

According to the Institute of Medicine\(^1\) in Washington, DC, preventable adverse events in the United States, including hospital-acquired infections, are responsible for 44,000 to 98,000 deaths annually and represent a cost of $17 to $29 billion. As precise epidemiologic data about these events are sparse, this estimation was extrapolated from two studies only.\(^2\)\(^–\)\(^5\) This report has generated a consid-

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*Infection Control in the ICU*
Nosocomial infections (NIs) affect >2 million persons annually in the United States and concern 5 to 35% of patients who are admitted to ICUs. They are viewed as an inexorable tribute to pay to the more aggressive management of the population, characterized by the use of sophisticated technologies and invasive devices. The pathophysiology of NIs includes colonization of the host by potentially dangerous pathogens, such as microorganisms from exogenous or endogenous sources, including resistant strains such as methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant enterococci (VRE), azole-resistant Candida spp, and extended-spectrum β-lactamase (ESBL) Gram-negative pathogens. Ventilator-associated pneumonia, catheter-related bloodstream infections, surgical site infections (SSIs), and urinary catheter-related infections account for >80% of NIs.

The Study on the Efficacy of Nosocomial Infection Control (SINTONIC),
from the CDC has suggested that at least one third of NIs are preventable through infection control programs, which have been implemented in most centers during the last 2 decades. Risk factors are well-identified and have been the target of efficient preventive measures. This may explain why NI rates are now included in the criteria used for assessing the quality of patient care in many institutions. Control and prevention include general measures such as hand hygiene, isolation and restriction of antibiotic use, and more specific measures that have been demonstrated to be efficient in reducing particular types of NIs.

DEFINITIONS

NI schematically encompasses any infection that is neither present nor incubating on hospital admission. Precise definitions have been largely debated in the literature, but those proposed by the CDC in 1988 have been validated and are now widely used. Minor adaptations are generally proposed for specific populations, but infections are considered to be hospital-acquired if they develop at least 48 h after hospital admission without proven prior incubation. If infections occur up to 3 days after hospital discharge or within 30 days of an operative procedure, they are attributed to the admitting hospital or ward, or to the surgical procedure, respectively.

A specific terminology is used to describe the epidemiology of NIs. The prevalence of infected patients is defined as the number of patients with an active infection divided by the total number of patients who are present at the time of the survey. The prevalence of infection is the number of active infections divided by the total number of patients who are present at the time of the survey. The incidence of infected patients is defined as the number of patients who developed any infection divided by the total number of patients at risk who are hospitalized in the ward concerned during a determined period of time. Once infected, patients cannot be considered at risk of infection. The incidence of infection is defined as the number of infectious episodes divided by the total number of patients who were hospitalized in the concerned ward during a determined period of time. The incidence-density of infection/infected patients refers to the number of infectious episodes/infected patients per 1,000 patient-days at risk. The latter is the most appropriate way to express infection rates and to measure the impact of preventive strategies. However, this approach mandates the prospective surveillance of all patients who are at risk for NIs with individual records of events considered both in the numerator and the denominator.

EPIDEMIOLOGY OF NIs

Epidemiologic data collected from surveillance activities are used to determine NI rates. Benchmarking then may be used to monitor their evolution and to detect any unusual variation that may be potentially suspect of outbreaks or high endemic rates of NI. Importantly, NI rates vary widely according to the type of ICU and the population served. They may also vary with the type of surveillance (Table 1). A prevalence of 20.6% was reported by Vincent et al.

A prevalence of 9.2%, corresponding to an incidence density of 23.7 episodes per 1,000 patient-days, was reported for the 164,034 patients in 119 ICUs surveyed from 1986 through 1990 in the NNIS system. A specific terminology is used to describe the epidemiology of NIs. The prevalence of infected patients is defined as the number of patients with an active infection divided by the total number of patients who are present at the time of the survey. The prevalence of infection is the number of active infections divided by the total number of patients who are present at the time of the survey. The incidence of infected patients is defined as the number of patients who developed any infection divided by the total number of patients at risk who are hospitalized in the ward concerned during a determined period of time. Once infected, patients cannot be considered at risk of infection. The incidence of infection is defined as the number of infectious episodes divided by the total number of patients who were hospitalized in the concerned ward during a determined period of time. The incidence-density of infection/infected patients refers to the number of infectious episodes/infected patients per 1,000 patient-days at risk. The latter is the most appropriate way to express infection rates and to measure the impact of preventive strategies. However, this approach mandates the prospective surveillance of all patients who are at risk for NIs with individual records of events considered both in the numerator and the denominator.
NIs developed in 7.8% of hospitalized patients (14,177 of 181,993 patients), corresponding to an incidence density of 19.8 episodes per 1,000 patient-days. UTIs (31%) were the most common, with 95% occurring in catheterized patients. Pneumonia, which was ventilator-associated in 86% of cases, represented 19% (laboratory-confirmed, 18.2%, and clinical sepsis, 0.8%), of which 87% were found to be catheter-related. NI device-related rates (ie, catheter-related UTI, central venous catheter-related bloodstream infections, and ventilator-associated pneumonia) were 5.5, 4.0, and 7.1, respectively, episodes per 1,000 device-days for coronary ICUs, 6.4, 5.3, and 6.8, respectively, for medical ICUs, 4.8, 6.9, and 4.0, respectively, for pediatric ICUs, and 4.6, 5.1, and 12.5, respectively, for surgical ICUs. Comparable incidences of NIs have been reported in ICUs from other developed countries. Moreover, preliminary data from the NNIS system suggest that risk-adjusted NI rates decreased over time for these three infections that are continuously monitored in ICUs.

**Impact of NIs**

A significant correlation was found between the prevalence rate of ICU-acquired infection and mortality rate. In the European Prevalence of Infection in Intensive Care study, laboratory-proven bloodstream infection (odds ratio [OR], 1.73; 95% confidence interval [CI], 1.25 to 2.41), pneumonia (OR, 1.91; 95% CI, 1.6 to 2.29), and clinical sepsis (OR, 3.75; 95% CI, 1.71 to 7.18) were independently associated with a significant increase in mortality.
associated with an increased mortality rate. Additional independent predictors of death were an acute physiology and chronic health evaluation (APACHE) II score > 20 (OR, 15.6; 95% CI, 9.3 to 26), prolonged (≥ 21 days) ICU stay (OR, 2.52; 95% CI, 1.99 to 3.18), age > 60 years (OR for age 60 to 69 years, 1.7; 95% CI, 1.07 to 2.71; OR for age ≥ 70 years, 2.08; 95% CI, 1.31 to 3.31), the presence of organ failure on hospital admission (OR, 1.68; 95% CI, 1.45 to 19.5), and cancer as comorbidity (OR, 1.68; 95% CI, 1.4 to 2.0).

The analysis of the impact of NIs on health care revealed that they are responsible for a significant increase in mortality, morbidity, length of hospital and ICU stay, and resource utilization in almost all of the groups of patients studied (Table 4). After implementation of a global program targeted at the reduction of vascular access-related infections. Bloodstream infections include episodes of primary bacteremia (1.2/1,000 patient-days) and of clinical sepsis (2.6/1,000 patients-days).

Data adapted from reports of the NNIS database. The impact is determined by the attributable part of the mortality. The appropriateness of the evaluation protocol is another direct method that is used to estimate the prolongation of the length of hospital stay. Based on standardized criteria, the patient is evaluated daily to determine whether the stay in the hospital is related to the underlying disease and/or to the presence of an NI. Another method compares two groups of patients, one with a specified NI and one without a specified NI. Differences are expected to be attributable to the NI. However, this technique does not take into consideration potential confounding parameters that may exist between the two groups of patients. This effect can be attenuated by including factors potentially related to death in multivariate analysis. Nonetheless, these adjustments are generally insufficient and the attributable part is often overestimated. The so-called case-controlled studies (ie, those called, more appropriately, historical cohort studies with matching on potential confounders) are considered to be the best way to determine the impact of NIs. Infected and noninfected patients are carefully matched for several confounding factors related to the parameter investigated (eg, age, severity of underlying disease, associated comorbidities, and time of exposure to risk factors). Biased evaluations of the impact are

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of ICU</th>
<th>Units, No.</th>
<th>Patients, No.</th>
<th>Infections, No.</th>
<th>Overall</th>
<th>Bloodstream</th>
<th>Respiratory</th>
<th>Urinary</th>
<th>Wound/Soft Tissue</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Richards et al²⁴</td>
<td>Medical</td>
<td>112</td>
<td>181,903</td>
<td>14,177</td>
<td>19.8</td>
<td>3.8</td>
<td>5.3</td>
<td>6.1</td>
<td>NE</td>
<td>4.6</td>
</tr>
<tr>
<td>Eggmann et al²⁴</td>
<td>Medical</td>
<td>1</td>
<td>1,050</td>
<td>145</td>
<td>34.0</td>
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<td>12.7</td>
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<td>7.0</td>
<td>2.1</td>
</tr>
<tr>
<td>Brooks et al³⁶</td>
<td>Medical</td>
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<td>180</td>
<td>12</td>
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<td>4.1</td>
<td>1.0</td>
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<tr>
<td>Richards et al²⁴</td>
<td>Pediatric</td>
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<td>6,290</td>
<td>14.1</td>
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<td>1.4</td>
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<tr>
<td>Raymonod and Anjard³⁸</td>
<td>Pediatric</td>
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<td>710</td>
<td>168</td>
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<tr>
<td>Gastmeier et al³⁹</td>
<td>Pediatric</td>
<td>72</td>
<td>515</td>
<td>78</td>
<td>15.3</td>
<td>2.1</td>
<td>8.9</td>
<td>2.3</td>
<td>NE</td>
<td>2.0</td>
</tr>
<tr>
<td>Simon et al⁴⁰</td>
<td>Pediatric</td>
<td>1</td>
<td>201</td>
<td>15</td>
<td>15.7</td>
<td>4.8</td>
<td>6.8</td>
<td>1.9</td>
<td>0.8</td>
<td>0.0</td>
</tr>
<tr>
<td>Gilo et al⁴¹</td>
<td>Pediatric</td>
<td>1</td>
<td>500</td>
<td>65</td>
<td>31.7</td>
<td>1.5</td>
<td>12.7</td>
<td>4.4</td>
<td>4.4</td>
<td>8.7</td>
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<tr>
<td>Legras et al⁴²</td>
<td>Mixed</td>
<td>5</td>
<td>1,589</td>
<td>344</td>
<td>20.3</td>
<td>4.1</td>
<td>5.7</td>
<td>5.2</td>
<td>NE</td>
<td>5.2</td>
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<tr>
<td>Koffel et al⁴⁴</td>
<td>Mixed</td>
<td>2</td>
<td>2,000</td>
<td>286</td>
<td>32.3</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>Doebbeling et al⁴⁵</td>
<td>Mixed</td>
<td>3</td>
<td>2,734</td>
<td>354</td>
<td>44.3</td>
<td>2.5</td>
<td>22.7</td>
<td>6.9</td>
<td>4.3</td>
<td>7.1</td>
</tr>
<tr>
<td>Barsic et al⁴⁶</td>
<td>Mixed</td>
<td>1</td>
<td>660</td>
<td>688</td>
<td>57.1</td>
<td>22.8</td>
<td>21.8</td>
<td>12.5</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>Price et al⁴⁷#</td>
<td>Surgical</td>
<td>1</td>
<td>139</td>
<td>49</td>
<td>11.5</td>
<td>0.0</td>
<td>9.2</td>
<td>2.3</td>
<td>1.5</td>
<td>0.0</td>
</tr>
<tr>
<td>Koffel et al⁴⁶</td>
<td>Surgical</td>
<td>1</td>
<td>327</td>
<td>54</td>
<td>47.2</td>
<td>9.6</td>
<td>15.8</td>
<td>NE</td>
<td>NE</td>
<td>18.3</td>
</tr>
<tr>
<td>Velasco et al⁴⁷</td>
<td>Urology</td>
<td>1</td>
<td>623</td>
<td>370</td>
<td>91.7</td>
<td>22.1</td>
<td>26.5</td>
<td>23.5</td>
<td>NE</td>
<td>19.6</td>
</tr>
<tr>
<td>Richards et al⁴⁸</td>
<td>Coronary</td>
<td>93</td>
<td>227,451</td>
<td>6,608</td>
<td>10.6</td>
<td>1.8</td>
<td>2.6</td>
<td>3.7</td>
<td>NE</td>
<td>2.5</td>
</tr>
<tr>
<td>Wurtz et al⁴⁹</td>
<td>Burn</td>
<td>1</td>
<td>57</td>
<td>36</td>
<td>32.3</td>
<td>1.8</td>
<td>19.7</td>
<td>9.0</td>
<td>0.9</td>
<td>0.9</td>
</tr>
</tbody>
</table>

*NE = data could not be extracted from the original publication.
†Data adapted from reports of the NNIS database.
‡After implementation of a global program targeted at the reduction of vascular access-related infections. Bloodstream infections include episodes of primary bacteremia (1.2/1,000 patient-days) and of clinical sepsis (2.6/1,000 patients-days).
¶Bloodstream infections include episodes of primary bacteremia (1.9/1,000 patient-days).
§Bloodstream infections include episodes of primary bacteremia (3.0/1,000 patient-days).
††Patients hospitalized for severe infections over a 6-year period.
#Data reported are insufficient to extract details on incidence-densities for each type of infection.
Identified in several studies (Table 5).

Ventilatory strategies.

Physicians who have to select and implement preventive strategies.

Concerns not only epidemiologists but, also, ICU literature regarding the attributable mortality of NIs which imply that the controversies in the recent Cost-effectiveness analysis is based on these data, enormous differences reported between the studies may be related to some confusion between the associated and the differences may be identified. Apart from the overall risk factors for NIs, more specific risk factors have been delineated from numerous studies designed to identify those associated with specific infections.

Among them, the severity of underlying illness assessed by scoring systems such as APACHE II/III or simplified acute physiologic score II are the most widely used. However, these scores were designed to predict mortality and are less consistent predictors of NIs. These general scores also may be of limited value in the field of sepsis. In a series of 88 consecutive patients with septic shock, we found a low predictive value for APACHE II and simplified acute physiologic II scores. A prolonged length of stay, mechanical ventilation, and the use of vascular accesses also were identified. Apart from the overall risk factors for NIs, more specific risk factors have been delineated from numerous studies designed to identify those associated with specific infections.

Understaffing and overcrowding in ICUs have been reported to increase the risk of human errors, iatrogenic complications, and even death. They have also played an important role in several outbreaks and are to be considered as potential risk factors for the acquisition of NIs. Franks et al reported an outbreak of catheter-related bloodstream infections that apparently were associated with total parenteral nutrition in critically ill surgical patients. After adjustment for confounding parameters (ie, type of nutrition, mechanical ventilation, and

### Table 3—Device-Associated Rates of NIs in the ICUs During the 1990s*

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of ICU</th>
<th>Period</th>
<th>Units, No.</th>
<th>Bloodstream Infections/1,000 CVC-Days, No.</th>
<th>Ventilator-Associated Pneumonia/1,000 Ventilator-Days, No.</th>
<th>UTIs/1,000 Catheter-Days, No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>NNIS 50</td>
<td>Medical</td>
<td>1997–1999</td>
<td>135</td>
<td>5.3 (3.6–7.1)</td>
<td>6.8 (4.1–9.9)</td>
<td>6.4 (3.6–8.8)</td>
</tr>
<tr>
<td>NNIS 50</td>
<td>Coronary</td>
<td>1997–1999</td>
<td>112</td>
<td>4.0 (1.7–6.3)</td>
<td>7.1 (3.9–12.2)</td>
<td>5.5 (3.1–9.8)</td>
</tr>
<tr>
<td>Eggimann et al 24</td>
<td>Medical</td>
<td>1997</td>
<td>1</td>
<td>2.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Richards et al 41</td>
<td>Mixed†</td>
<td>1992–1995</td>
<td>135</td>
<td>3.6 (1.8–5.2)</td>
<td>9.8 (6.9–13.0)</td>
<td>4.2 (0.8–5.9)</td>
</tr>
<tr>
<td>Richards et al 41</td>
<td>Mixed†</td>
<td>1992–1995</td>
<td>69</td>
<td>5.9 (4.0–7.8)</td>
<td>11.1 (7.2–16.0)</td>
<td>6.8 (2.5–9.9)</td>
</tr>
<tr>
<td>Gastmeier et al 30</td>
<td>Mixed</td>
<td>1994</td>
<td>59</td>
<td>4.9</td>
<td>12.7</td>
<td>6.1</td>
</tr>
<tr>
<td>Legras et al 32</td>
<td>Mixed</td>
<td>1995</td>
<td>5</td>
<td>4.8</td>
<td>9.4</td>
<td>4.2</td>
</tr>
<tr>
<td>Barsic et al 41</td>
<td>Mixed</td>
<td>1990–1997</td>
<td>1</td>
<td>11.3</td>
<td>35.1</td>
<td>13.4</td>
</tr>
<tr>
<td>Khuri-Bulos et al 52</td>
<td>Mixed</td>
<td>1993–1995</td>
<td>1</td>
<td>3.0</td>
<td>19.1</td>
<td>15.6</td>
</tr>
<tr>
<td>Finkelstein et al 31</td>
<td>Mixed</td>
<td>1997–1999</td>
<td>1</td>
<td>12.0</td>
<td>20.0</td>
<td>14.0</td>
</tr>
<tr>
<td>NNIS 50</td>
<td>Surgical</td>
<td>1997–1999</td>
<td>157</td>
<td>5.1 (2.6–7.0)</td>
<td>12.5 (8.4–16.0)</td>
<td>4.6 (3.3–7.6)</td>
</tr>
<tr>
<td>Wallace et al 34</td>
<td>Surgical</td>
<td>1995–1997</td>
<td>1</td>
<td>8.0</td>
<td>16.7</td>
<td>7.8</td>
</tr>
<tr>
<td>Wallace et al 34</td>
<td>Trauma</td>
<td>1995–1997</td>
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<td>9.1</td>
<td>23.9</td>
<td>7.4</td>
</tr>
<tr>
<td>Khuri-Bulos et al 52</td>
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<td>1993–1995</td>
<td>1</td>
<td>42.9</td>
<td></td>
<td>11.8</td>
</tr>
<tr>
<td>Dettenkofer et al 35</td>
<td>Neurosurgical</td>
<td>1997–1998</td>
<td>1</td>
<td>0.9</td>
<td>15.1</td>
<td>8.5</td>
</tr>
<tr>
<td>Richards et al 37</td>
<td>Pediatric</td>
<td>1992–1997</td>
<td>61</td>
<td>7.9 (4.3–10.0)</td>
<td>6.0 (1.8–7.9)</td>
<td>5.4 (2.4–7.8)</td>
</tr>
<tr>
<td>NNIS 50</td>
<td>Pediatric</td>
<td>1997–1999</td>
<td>73</td>
<td>6.9 (4.1–9.3)</td>
<td>4.0 (1.2–7.6)</td>
<td>4.8 (2.0–7.0)</td>
</tr>
<tr>
<td>Gastmeier et al 37</td>
<td>Pediatric</td>
<td>1994–1995</td>
<td>73</td>
<td>12.5 (5.7–24.7)</td>
<td>3.1 (0.6–9.8)</td>
<td></td>
</tr>
<tr>
<td>Sing-Naz et al 36</td>
<td>Pediatric</td>
<td>1993</td>
<td>1</td>
<td>8.9</td>
<td>2.7</td>
<td>6.6</td>
</tr>
<tr>
<td>Sing-Naz et al 36</td>
<td>Pediatric</td>
<td>1995</td>
<td>1</td>
<td>16.8</td>
<td>2.7</td>
<td>6.2</td>
</tr>
<tr>
<td>Simon et al 39</td>
<td>Pediatric</td>
<td>1997–1998</td>
<td>1</td>
<td>8.0</td>
<td>5.7</td>
<td>5.2</td>
</tr>
<tr>
<td>Simon et al 39</td>
<td>Pediatric</td>
<td>1998</td>
<td>1</td>
<td>10.7</td>
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<tr>
<td>Khuri-Bulos et al 52</td>
<td>Neonatal</td>
<td>1993–1995</td>
<td>1</td>
<td>24.4</td>
<td>23.9</td>
<td></td>
</tr>
<tr>
<td>Weber et al 38</td>
<td>Burn</td>
<td>1990–1991</td>
<td>1</td>
<td>4.9</td>
<td>11.4</td>
<td>13.2</td>
</tr>
</tbody>
</table>

*Values given as 50th percentile (25th to 75th percentile), unless otherwise indicated.
†Nonmajor teaching hospitals.
‡Major teaching hospitals.

Risk Factors

Independent risk factors for NIs have been identified in several studies (Table 5). Among them, the severity of underlying illness assessed by scoring systems such as APACHE II/III or simplified acute physiologic score II are the most widely used. However, these scores were designed to predict mortality and are less consistent predictors of NIs. These general scores also may be of limited value in the field of sepsis. In a series of 88 consecutive patients with septic shock, we found a low predictive value for APACHE II and simplified acute physiologic II scores. A prolonged length of stay, mechanical ventilation, and the use of vascular accesses also were identified. Apart from the overall risk factors for NIs, more specific risk factors have been delineated from numerous studies designed to identify those associated with specific infections.

Understaffing and overcrowding in ICUs have been reported to increase the risk of human errors, iatrogenic complications, and even death. They have also played an important role in several outbreaks and are to be considered as potential risk factors for the acquisition of NIs. Fridkin et al reported an outbreak of catheter-related bloodstream infections that apparently were associated with total parenteral nutrition in critically ill surgical patients. After adjustment for confounding parameters (ie, type of nutrition, mechanical ventilation, and
duration of hospitalization), the patient-to-nurse ratio was found to be a major independent risk factor. As compared with a patient-to-nurse ratio of 1, the relative risks (RRs) were 3.95 (95% CI, 1.07 to 14.5), 16.6 (95% CI, 1.15 to 211), and 61.5 (95% CI, 1.23 to 3,074) for ratios of 1.2, 1.5, and 2, respectively. In our sophisticated ICU environments, many factors contribute to the development of NIs, but complex, careful investigation may identify precise factors that may be simple to correct. We highlighted the importance of understaffing and overcrowding during an outbreak of serious Enterobacter cloacae infections in a neonatal ICU. Molecular studies demonstrated that eight patients (5.73 episodes per 1,000 patient-days as compared with 0.86 episodes per 1,000 patient-days for the preceding 21-month period), representing 13.3% of infants who were hospitalized over a 2-month period, were infected by three epidemic clones. Cross-transmission was facilitated by understaffing (57% of required personnel) and overcrowding (166% of theoretical capacity) with an increased risk of E cloacae carriage during the outbreak period as compared with the control period (OR, 16.3; 95% CI, 1.8 to 16.3). The outbreak was stopped after a decrease in workload, reinforcement of single-dose medication, and increased compliance with hand hygiene before IV line handling, which rose from 25% to 70%.

Pathophysiology of NIs

The colonization of the host by potentially pathogenic microorganisms is a prerequisite for the further development of most NIs and may occur from exogenous or endogenous sources. As a consequence of the severity of the underlying diseases with possibly impaired host defenses, and in the presence of risk factors, critically ill patients are particularly susceptible to a rapid colonization by endemic pathogens of the hospital flora. The endemic transmission of exogenous staphylococci and other potential pathogens by the hands of health-care workers (HCWs) is well-documented. Goldmann et al reported the presence of Gram-negative bacilli on the hands of 75% of neonatal ICU personnel. A report from the National Institute of Health.

Table 4—Impact of NIs in Critical Care

<table>
<thead>
<tr>
<th>Type of Infection</th>
<th>Study</th>
<th>Crude Mortality, %</th>
<th>Attributable Mortality, %</th>
<th>Prolongation of Length of Stay, d*</th>
<th>Attributable Costs, $†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any NIs</td>
<td></td>
<td></td>
<td></td>
<td>ICU</td>
<td>Hospital</td>
</tr>
<tr>
<td>All sites of infections</td>
<td>Bjerke et al82</td>
<td>27.8</td>
<td>21.6</td>
<td>23.0</td>
<td></td>
</tr>
<tr>
<td>All sites of infections</td>
<td>Bueno-Cavanillas et al83</td>
<td>27.9</td>
<td>16.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All sites of infections</td>
<td>Girou et al84</td>
<td>82.0</td>
<td>44.0</td>
<td>14.5</td>
<td></td>
</tr>
<tr>
<td>All sites of infections</td>
<td>Gilio et al85</td>
<td>10.9</td>
<td>2.8</td>
<td>6.0</td>
<td></td>
</tr>
<tr>
<td>Bloodstream infections</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Catheter-related bloodstream</td>
<td>Soufir et al85</td>
<td>50.0</td>
<td>28.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Catheter-related bloodstream</td>
<td>Rello et al86</td>
<td>22.4</td>
<td>34.7</td>
<td>19.7</td>
<td>3,500</td>
</tr>
<tr>
<td>Catheter-associated bloodstream</td>
<td>Pittet and Wenzel87</td>
<td>45.0</td>
<td>25.0</td>
<td>6.5</td>
<td>29,000</td>
</tr>
<tr>
<td>Primary bacteremia</td>
<td>Smith et al88</td>
<td>82.4</td>
<td>29.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary bacteremia</td>
<td>DiGiovine et al89</td>
<td>35.3</td>
<td>4.4</td>
<td>10.0</td>
<td>34,000</td>
</tr>
<tr>
<td>Primary bacteremia</td>
<td>Wispelinghoff et al90</td>
<td>31.0</td>
<td>16.0</td>
<td>20.0</td>
<td></td>
</tr>
<tr>
<td>Bacteremia (primary and secondary)</td>
<td>Rello et al91</td>
<td>31.5</td>
<td>20.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bacteremia (primary and secondary)</td>
<td>Forgacs et al94</td>
<td>60.4</td>
<td>47.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bacteremia (primary and secondary)</td>
<td>Pittet et95</td>
<td>50.0</td>
<td>35.0</td>
<td>8.0</td>
<td>24.0</td>
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<tr>
<td>Respiratory tract infections</td>
<td></td>
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<td></td>
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<tr>
<td>Pneumonia (hospital and ICU)</td>
<td>Craig and Connelly74</td>
<td>20.0</td>
<td>15.0</td>
<td>11.0</td>
<td></td>
</tr>
<tr>
<td>Pneumonia (hospital and ICU)</td>
<td>Leu et75</td>
<td>20.3</td>
<td>7.1</td>
<td>9.2</td>
<td></td>
</tr>
<tr>
<td>Ventilator-associated pneumonia</td>
<td>Fagon et76</td>
<td>71.0</td>
<td>42.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ventilator-associated pneumonia</td>
<td>Fagon et77</td>
<td>52.4</td>
<td>30.0</td>
<td>23.0</td>
<td></td>
</tr>
<tr>
<td>Ventilator-associated pneumonia</td>
<td>Heyland et78</td>
<td>23.7</td>
<td>7.8</td>
<td>6.5</td>
<td></td>
</tr>
<tr>
<td>UTIs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary bacteremia</td>
<td>Platt et99</td>
<td>19.0</td>
<td>4.0</td>
<td>3.0</td>
<td></td>
</tr>
</tbody>
</table>

*For patients surviving the infection.
†Costs attributed to the infection in surviving patients.
‡Attributable mortality was not determined in a matched-control study but by simple comparison with the crude mortality of all patients who did not develop a bloodstream infection.
A continuous shift toward more resistant strains of bacteria has been reported for several decades. Concern has focused on MRSA, VRE, ESBLs, fluoroquinolone-resistant *Pseudomonas aeruginosa*, and fluconazole-resistant *Candida* spp. These pathogens have become the leading causes of NIs, particularly in ICUs where most were found to have a certain specificity according to the type of ICU. The predominant pathogens reported in the ICUs participating in the NNIS and in European countries are coagulase-negative staphylococci (CoNS), *S. aureus, P. aeruginosa*, enterococci, and *Candida* spp (Table 6).

The factors responsible for this evolution are not fully understood, but antibiotic pressure certainly plays a major role. Studies have repetitively demonstrated that antibiotic exposure, particularly to cephalosporins, constitutes an independent risk factor for colonization and infection with both resistant Gram-positive cocci and Gram-negative bacilli in ICUs. This selective pressure was recently emphasized by Harbarth et al in their elegant analysis of the impact of cephalosporin-based prophylaxis in a cohort of 2,641 consecutive patients who had been referred for heart surgery over a 5-year period. As compared to short-term prophylaxis, prolonged prophylaxis (*ie*, >48 h) was not associated with a decreased risk of SSI but was clearly correlated with an increased risk of colonization with resistant microorganisms.

A further relationship between antibiotic resistance and antibiotic use in ICUs is strongly suggested for some pathogens by a prospective survey in 41 hospitals included in phase 2 of the Intensive Care Antimicrobial Resistance Epidemiology project. Average antimicrobial use, which was expressed as the daily defined dose per 1,000 patient-days, revealed that first-generation and third-generation cephalosporins and parenteral vancomycin were the most commonly used agents in the ICUs included in the project. The demographics of these hospitals were similar to the 221 other institutions participating in the NNIS system, and susceptibility could be analyzed for isolates collected over a 12-month period. The highest resistance rates occurred among isolates from ICU patients, followed in decreasing order by those from non-ICU patients and outpatients. These organisms included the following: methicillin-resistant CoNS (resistance rates, 75%, 60.4%, and 44.5%, respectively); MRSA (resistance rates, 35.2%, 31.9%, and 17.7%, respectively); VRE (resistance rates, 13.0%, 11.8%, and 2.5%, respectively); piperacillin-resistant *P. aeruginosa* (resistance rates, 12.2%, 8.3%, and

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**Microbiology**

**Table 5—Overall Risk Factors Associated with the Acquisition of NIs in ICU**

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Study</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severity score</td>
<td>Vincent et al*</td>
<td>15.6</td>
<td>9.3–26.00</td>
</tr>
<tr>
<td></td>
<td>Girou et al†</td>
<td>2.68</td>
<td>1.05–6.89</td>
</tr>
<tr>
<td></td>
<td>Singh-Naz et al‡</td>
<td>1.60</td>
<td>1.50–1.78</td>
</tr>
<tr>
<td>Shock on admission</td>
<td>Craven et al§</td>
<td>1.7</td>
<td>1.2–2.5</td>
</tr>
<tr>
<td>Prolonged length of ICU stay</td>
<td>Vincent et al‡</td>
<td>1.13</td>
<td>1.0–1.15</td>
</tr>
<tr>
<td></td>
<td>Leon-Rossales et al†</td>
<td>1.12</td>
<td>1.02–1.23</td>
</tr>
<tr>
<td></td>
<td>Singh-Naz et al‡</td>
<td>4.3</td>
<td>3.8–4.8</td>
</tr>
<tr>
<td></td>
<td>Gilio et al‡</td>
<td>1.71</td>
<td>1.31–2.14</td>
</tr>
<tr>
<td></td>
<td>Craven et al§</td>
<td>2.5</td>
<td>1.9–3.4</td>
</tr>
<tr>
<td>Age &gt; 60 years</td>
<td>Legras et al‡</td>
<td>1.54</td>
<td>1.08–2.16</td>
</tr>
<tr>
<td>Size of the unit (&gt; 10 beds)</td>
<td>Vincent et al‡</td>
<td>1.3</td>
<td>1.07–1.85</td>
</tr>
<tr>
<td>Parenteral nutrition</td>
<td>Singh-Naz et al‡</td>
<td>22.1</td>
<td>7.1–68.8</td>
</tr>
<tr>
<td></td>
<td>Gilio et al‡</td>
<td>2.47</td>
<td>1.05–5.81</td>
</tr>
<tr>
<td>Antimicrobial therapy</td>
<td>Singh-Naz et al‡</td>
<td>5.21</td>
<td>2.0–13.6</td>
</tr>
<tr>
<td>Central venous access</td>
<td>Vincent et al‡</td>
<td>4.6</td>
<td>3.12–6.8</td>
</tr>
<tr>
<td></td>
<td>Legras et al‡</td>
<td>3.18</td>
<td>2.12–4.75</td>
</tr>
<tr>
<td>Days with arterial line</td>
<td>Craven et al‡</td>
<td>1.1</td>
<td>1.05–1.11</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>Vincent et al‡</td>
<td>1.75</td>
<td>1.51–2.03</td>
</tr>
<tr>
<td></td>
<td>Koffel et al†</td>
<td>1.13</td>
<td>1.1–1.16</td>
</tr>
<tr>
<td>Tracheostomy</td>
<td>Koffel et al†</td>
<td>2.1</td>
<td>1.54–2.85</td>
</tr>
<tr>
<td>Device utilization ratio</td>
<td>Singh-Naz et al‡</td>
<td>2.36</td>
<td>1.6–3.5</td>
</tr>
<tr>
<td></td>
<td>Gilio et al‡</td>
<td>1.6</td>
<td>1.1–2.35</td>
</tr>
<tr>
<td></td>
<td>Legras et al‡</td>
<td>3.2</td>
<td>2.3–4.5</td>
</tr>
<tr>
<td>Neurologic failure at day 3</td>
<td>Girou et al‡</td>
<td>1.34</td>
<td>1.09–1.64</td>
</tr>
<tr>
<td></td>
<td>Leon-Rossales et al‡</td>
<td>1.7</td>
<td>1.01–2.84</td>
</tr>
<tr>
<td>Intracranial pressure monitor</td>
<td>Craven et al‡</td>
<td>2.5</td>
<td>1.1–5.9</td>
</tr>
</tbody>
</table>

*APACHE II score.
†Pediatric risk of mortality score; pediatric critically ill patients.
‡Per stay > 20 days: 2.53 (CI, 1.99 to 3.18).
§Three to 10 days vs 3 days.
∥Device utilization ratio = (95% catheter-days + urinary catheter-days + mechanical ventilation-days)/length of stay.

Epidemiology of Mycoses Survey with surveillance cultures systematically performed on the hands of HCWs from 13 ICUs showed that 33% of patients (range, 18 to 58%) in adult ICUs and 29% of patients (range, 8 to 62%) in pediatric ICUs were positive for *Candida* spp over an 18-month period. Importantly, the hands of HCWs are only transiently contaminated and, as discussed later, appropriate hand hygiene measures are sufficient to remove the organisms and to stop the transmission.

Many NIs are believed to arise from the endogenous flora of the skin, oropharyngeal, or GI tracts due to treatments such as chemotherapy, corticosteroid therapy, or antibiotic therapy, and also by the use of invasive devices such as intravascular or urinary catheters and nasogastric or endotracheal tubes. This flora also is responsible for the majority of surgical wound infections.

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(6.0% respectively); and ceftazidime-resistant, cefotaxime-resistant, or ceftriaxone-resistant Enterobacter spp (resistance rates, 25.0%, 22.3%, and 10.1%, respectively). All these stepwise decreases were statistically significant. In contrast, this was not the case for penicillin-resistant pneumococci (resistance rates, 9.5%, 10.4%, and 9.8%, respectively) or for fluoroquinolone-resistant P aeruginosa (resistance rates, 16.4%, 17.6%, and 20.0%).

Apart from fluoroquinolones, which may have a similar exposure in both parts of the hospital, for each of the antimicrobial groups used at higher levels in ICUs there was a correspondingly higher rate of resistant pathogens among isolates from the ICU compared with non-ICU patients. Several reports also have demonstrated the spread of antibiotic resistance from ICUs to other hospital wards.

S aureus and CoNS

Currently, > 60% of CoNS isolates and nearly 20% of S aureus isolates from ICUs are resistant not only to methicillin, but also to several other agents such as aminoglycosides, tetracyclines, and quinolones. Although not associated with higher mortality rates, compared with infections due to methicillin-sensitive S aureus, bacteremia due to MRSA may be more difficult to treat. The proportion of cases in which MRSA is responsible for NIs in critically ill patients reported to the NNIS system increased from < 30% in 1989 to up to 40% in 1997. MRSA already accounts for 30% to > 50% of cases in some European ICUs, particularly in southern Europe and the Mediterranean area. Infection control measures rely on the interruption of cross-transmission by appropriate hand hygiene measures, isolation precautions, and the reduction of selective pressure by inappropriate antibiotic use.

Vancomycin-intermediate and glycopeptide-intermediate S aureus have emerged. Routine disk-diffusion for the determination of antibiotic resistance does not correctly identify these strains, which have to be suspected on an epidemiologic basis or in patients with staphylococcal infections and a poor response to despite adequate glycopeptide therapy. The precise mechanism responsible for the emergence of these strains has not been fully elucidated. The vanA, vanB, and vanC genes, which are responsible for glycopeptide-resistance acquisition among enterococci, were not isolated from these strains, suggesting a different mechanism of resistance. Epidemiologic data suggest that the increased use of glycopeptides in hospitalized patients may play a role in this evolution.

Infection control measures rely on the strict application of all the guidelines recommended for the prevention and control of MRSA.
The rate of VRE infection increased from 0.5% in 1989 to 22% in 1997 among ICU patients with NIs reported to the NNIS, and bacteremia due to enterococci may be particularly difficult to treat. Risk factors associated with the acquisition of gentamicin resistance by enterococci in a general hospital reported by Axelrod and Talbot included length of stay, mean duration of antibiotic therapy received, and admission to an ICU. GI colonization with VRE and the use of antimicrobial agents active against anaerobes were found by Edmond et al to be risk factors for the development of VRE bacteremia. This was recently confirmed by Donkey et al, who found that antianaerobic agents promoted high-density colonization with VRE. In an accompanying editorial, Wenzel and Edmond highlighted the importance of these findings, which support the concept of antibiotic pressure (i.e., the crude relationship between the extent of antibiotic use and the selection of resistant strains). VRE may be found in the stool samples of as many as 47% of asymptomatic patients after antibiotic administration.

ESBLs

Outbreaks of NIs caused by multiresistant Enterobacteriaceae have been reported. Brum-Buisson et al described an outbreak caused by Klebsiella pneumoniae that successively involved three ICUs in the same hospital. The resistance was plasmid-mediated. In a prospective study on the colonization of critically ill patients with ESBLs over a six-month period, De Champs et al identified prolonged ICU stay as a significant risk factor and reported a decrease in the number of colonized patients after a change in the antibiotic policy.

Other Gram-Negative Pathogens

The proportion of other Gram-negative bacilli, such as P aeruginosa resistant to third-generation cephalosporins or to carbapenems, has remained stable at around 15% in most centers. The NNIS system has reported that the incidence of fluoroquinolone-resistant P aeruginosa has increased from 5% in 1989 to up to 15% in 1997 among ICU patients with NIs. Ventilator-associated pneumonia due to these microorganisms has already been reported in some European centers to be associated with worse outcome.

Candida spp

In the United States, the rate of severe fungal infections increased from 2.0 to 3.8 episodes per 1,000 hospital admissions between 1980 and 1990 in 115 participating hospitals in the NNIS system, with Candida spp responsible for 78% of those episodes. During the same period of time, the incidence of candidemia increased fivefold in medical centers having > 500 beds and 2.2-fold in those with < 200 beds. Candida was responsible for 7.2% of bloodstream infections (10.2% in ICUs), preceded by enterococci, S aureus, and CoNS. Epidemiologic data from 1992 to 1997 indicate that fungal infections accounted for 12% of NIs. A 20-fold increase in the rate of candidemia was reported in a single institution where NIs were prospectively surveyed from 1981 through 1990. However, recent data suggest that this incidence may be stable in some other institutions.

The emergence of serious infections related to Candida glabrata and Candida krusei, which are mostly resistant to triazoles (fluconazole and itraconazole), was reported by bone-marrow transplant centers and some ICUs, where the proportion of these strains may represent > 50% of isolates from colonized patients. However, no such evolution has been reported in other institutions where the use of triazole prophylaxis was restricted to high-risk patients. The importance of these findings has to be balanced by the observation that the reduction of infections related to Candida albicans is largely superior to the increase of those related to intrinsically resistant strains of non-albicans Candida spp. Data from a surveillance program, which was designated to monitor the epidemiology of pathogens in 72 medical centers worldwide, indicate that C albicans remained largely predominant in the late 1990s. In fact, 97% of strains from European medical centers were susceptible to fluconazole; 86.5% were highly susceptible (minimum inhibitory concentration needed to kill 50% of isolates [MIC50], < 8 μg/mL), 10.6% were dose-related susceptible (MIC50, between 8 and 32 μg/mL), and 84% were susceptible to itraconazole (60.6% were highly susceptible [MIC50, < 8 μg/mL]; and 23.5% were dose-related susceptible [MIC50, 8 to 32 μg/mL]). These data confirmed those obtained in US medical centers where 75% of strains were hospital-acquired, including 44% from ICU patients.

Surveillance of NIs

The surveillance of NIs was recognized to be a major component of infection control in the late 1970s. The Study on the Efficacy of Nosocomial Infection Control showed that NI rates decreased on average 32% in hospitals where surveillance programs were implemented, compared with an
increase of 18% in other institutions over a 5-year period. The four key elements for successful prevention were the following: the presence of at least one epidemiologist for 1,000 beds; one specialized trained nurse for 250 beds; the existence of a planned surveillance system; and restitution of NI rates. Such programs were rapidly imposed in the United States as important criteria for hospital accreditation.155 Although less widespread than in the United States, infection control programs also were shown to be effective in Europe.156,157

Surveillance includes the following several distinct components: epidemiologic surveillance and intervention; administrative controls for medical equipment, for health-care personnel, and for patients; and engineering controls (Table 7). These have to be viewed as tools that have to be appropriately selected to solve specific problems.15,158

Epidemiologic surveillance is defined as the continuous collection, tabulation, analysis, and dissemination of all information on the occurrence of NIs in a specified ward and/or hospital.159 Several concepts have been developed, and the major advantages and disadvantages of specific tools are presented in Table 8. Total surveillance with the meticulous collection of clinical and microbiological data for each hospitalized patient is labor-intensive, time-consuming, and not always feasible on a practical basis.60 At the other end of the spectrum, the computerized surveillance of data from the microbiology laboratory alone gives limited information, which may be pertinent to a specific problem. Other types of computerized systems may be extremely helpful and may facilitate the rapid identification and handling of specific problems. For example, we implemented a fully computerized automatic alert system to identify at the time of hospital admission any patient in whom MRSA has been identified previously by the microbiology laboratory either during a previous hospital stay or during ambulatory care.25 This automatic alert system is now used to detect other resistant organisms and carriers.

In practical terms, a combined approach allows for the optimal use of resources.158 Continuous monitoring of different infections or microorganisms is mandatory to detect outbreaks that requires both specific and emergency measures.160 The surveillance of defined infections in particular wards or units may be useful for particular epidemiologic profiles and may help to design targeted programs to reduce the number of NIs.23,24,118,161 Administrative controls are guidelines that must be checked and executed by HCWs (Table 7). However, some controls are effective only if appropriate changes are incorporated into routine activities. We experienced a cluster of invasive pulmonary aspergillosis in non-immunocompromised critically ill patients associated with room air-filter replacement.162 Such fatal infections could have been prevented by the development and the application of guidelines for this procedure.

### CONTROL AND PREVENTION OF NIS

Prevention plays a major role in the control of NIs, and consensus conference and expert panels have

<table>
<thead>
<tr>
<th>Table 7—Elements of Surveillance Applied to Infection Control in Critical Care</th>
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<tbody>
<tr>
<td><strong>Elements of Surveillance</strong></td>
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<tr>
<td>Engineering controls</td>
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<td></td>
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<td></td>
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<tr>
<td>Administrative controls for medical equipment</td>
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<td>Administrative controls for healthcare personnel</td>
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<td>Administrative controls for patients</td>
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established numerous guidelines both in the United States and in European countries. These guidelines concern three main approaches, which can be schematized as follows. First, methods and techniques are needed to prevent cross-contamination and to control the potential sources of pathogens that could be transmitted from patient to patient or from HCW to patient. These methods and techniques include appropriate protocols for cleansing, disinfecting, and caring for various pieces of equipment and devices. Second, guidelines are needed for the appropriate use of surgical antibiotic prophylaxis or empirical therapy among selected groups of patients. Third, strategies to limit the emergence of resistant microorganisms need to be developed. In addition, specifically targeted measures against various types of NIs also have been proposed.

Isolation Precautions

More than 50% of patients who are admitted to ICUs already have been colonized at the time of admission with the microorganism responsible for subsequent infection; some patients will acquire it from the environment. The CDC has published guidelines on isolation precautions to minimize the risk of transmission of infectious agents from colonized/infected patients to other patients or HCWs. In brief, these guidelines are based on the application of the concepts of standard precautions (Table 9). Microorganisms may be transmitted by airborne droplet nuclei, by large-particle droplets, or by direct contact. Additional specific precautions are recommended accordingly (Table 10).

However, despite the fact that the use of guidelines has become a popular approach to improve the process of care, efforts to implement them in clinical practice often have been unsuccessful. Most requirements regarding infection control measures are unpopular and require restrictive procedures for which compliance is difficult to maintain, and it has been suggested that noncompliance is connected with the yearning of human beings for liberty. This is the case in the particular field of the MRSA pandemic, despite the fact that infection control measures have been proved to be efficacious and cost-effective. Noncompliance may be related to several aspects of human behavior, including the false perception of an invisible risk, the underestimation of individual responsibility in the epidemiology of the institution, passive attitudes regarding the increasing complexity of the process of care, and the negative impact of the socioeconomic constraints that are responsible for understaffing.

Local factors have to be taken into account to help to incorporate changes in the behavior of both the patients and the HCWs. As discussed in specific sections below, we have observed a strong positive impact in our institution after applying these concepts to the hospital-wide promotion of a bedside hand disinfection technique and to the implementation of an educational program targeted at vascular access care in the medical ICU.

Table 8—Concepts and Tools for Surveillance of NIs

<table>
<thead>
<tr>
<th>Surveillance Description</th>
<th>Sensitivity, %</th>
<th>Time Required, h/wk/500 Beds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Routine collection, tabulation, analysis, and dissemination of all information on the occurrence of NIs in a specified ward and/or hospital</td>
<td>74–94</td>
<td>36–54</td>
</tr>
<tr>
<td>Target-oriented Surveillance is restricted to priority-specific objectives, such as the control of the spread of MRSA or reduction of the incidence of catheter-related infections</td>
<td>77–91</td>
<td>23</td>
</tr>
<tr>
<td>Infection-specific Surveillance is limited to particular types of infections, such as outbreaks, or to specific laboratory data dealing with the resistance patterns of microbiological isolates</td>
<td>75–94</td>
<td>14–22</td>
</tr>
<tr>
<td>Tools</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chart review</td>
<td>Complete review of all charts, including laboratory data</td>
<td>7–56</td>
</tr>
<tr>
<td>Laboratory data</td>
<td>Identification of all patients with positive microbiological cultures</td>
<td>57</td>
</tr>
<tr>
<td>Ward documents review</td>
<td>Identification of patients at risk</td>
<td>70</td>
</tr>
<tr>
<td>Temperature</td>
<td>Identification of all patients with a body temperature ≥ 37.8°C</td>
<td>75</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Review of all patients receiving antibiotics</td>
<td>74</td>
</tr>
<tr>
<td>Temperature and antibiotics</td>
<td>Review of all patients with a body temperature ≥ 37.8°C and receiving antibiotics</td>
<td>75</td>
</tr>
<tr>
<td>Readmission</td>
<td>Review of all patients readmitted</td>
<td>75</td>
</tr>
<tr>
<td>Autopsy</td>
<td>Review of all autopsied patients</td>
<td>75</td>
</tr>
</tbody>
</table>

*NA = not available. Adapted from references 18, 34, 155, 158, and 316.
demonstrated that bacterial contamination of the HCWs is well-documented.\textsuperscript{91,94} The key role of HCWs hands in the transmission of pathogens from patient to patient was demonstrated 150 years ago by Ignaz Semmelweis. This obstetrician from Vienna was able to dramatically reduce the mortality related to puerperal fever by implementing systematic hand disinfection in chlorinated lime before examining patients.\textsuperscript{171} Since then, routine hand washing before and after patient contact remains the most important infection control measure.\textsuperscript{172,173}

The endemic transmission of exogenous staphylococci and other potential pathogens by the hands of HCWs is well-documented.\textsuperscript{91,94–97} This phenomenon is of particular concern in the ICU where patient care necessitates frequent contact. Goldmann et al\textsuperscript{98} reported the presence of Gram-negative bacilli on the hands of 75% of neonatal ICU personnel. As already mentioned, data have shown that one third to two thirds of the hands of HCWs in ICUs were found to be colonized by Candida spp.\textsuperscript{99} We have demonstrated\textsuperscript{174} that bacterial contamination of the hands increases linearly with time on ungloved hands during patient care (16 CFU (increase, 16 to 119 CFU), independent of the type of care provided and the hospital location.\textsuperscript{174} Updated guidelines for hand washing and/or hand disinfection were published by the Healthcare Infection Control Practices Advisory Committee (HICPAC)\textsuperscript{175} in 1995 (http://www.cdc.gov/ncidod/hip/sterile/sterile.htm). However, low-level compliance with hand hygiene has been systematically reported, particularly in ICUs where it does not exceed 40%.\textsuperscript{118,176–178} Several reasons have been suggested for such a low level of compliance, including the lack of priority over other required procedures, insufficient time, inconvenient placement of hand-washing facilities, allergy or intolerance to hand-hygiene solutions, and lack of leadership from senior medical staff.\textsuperscript{177,179–181} We have reported\textsuperscript{174} that compliance was inversely proportional to the number of opportunities per hour of patient care. In addition, those HCWs who do wash frequently and vigorously risk skin damage, which, ironically, results in the shedding of more organisms into the environment.\textsuperscript{182} Attempts to improve compliance with hand hygiene have been associated with some improvement.\textsuperscript{43,183} Only a few interventions have been associated with a sustained effect.\textsuperscript{25,184–186} The main parameters associated with successful improvement have been extensively discussed elsewhere (http://infection.thelancet.com), and examples based on published interventions are given herein.

Experience reported\textsuperscript{187} with alcohol-based handrubs suggested that hand disinfection reduces hand contamination more than hand washing. In a study published by Doebbeling et al,\textsuperscript{43} a hand-disinfection system using an antimicrobial agent (chlorhexidine) reduced the rate of NIs more effectively than one

### Table 9—Requirements for Standard Precautions* 

<table>
<thead>
<tr>
<th>Requirement</th>
<th>Field of Application</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hand hygiene</td>
<td>After direct contact with blood, body fluid, secretion, excretions, and contaminated items Immediately before gloving and after glove removal Between patient contacts and between dirty and clean body site contact in the same patient</td>
</tr>
<tr>
<td>Gloves</td>
<td>For anticipated contact with blood, body fluid, secretion, excretions, and contaminated items For anticipated contact with mucous membranes and nonintact skin</td>
</tr>
<tr>
<td>Mask, eye protection, face shield</td>
<td>To protect mucous membranes of the eyes, nose, and mouth during procedures and patient-care activities likely to generate splashes or sprays of blood, body fluid secretions, or excretions</td>
</tr>
<tr>
<td>Gowns</td>
<td>To protect skin and prevent soiling of clothing during procedures and patient-care activities likely to generate splashes or spray of blood, body fluid secretions, or excretions</td>
</tr>
<tr>
<td>Patient-care equipment</td>
<td>Soiled devices, linen, or clothing should be handled to prevent skin and mucous membrane exposure and transfer of microorganisms to the environment</td>
</tr>
<tr>
<td>Sharp objects</td>
<td>Avoid recapping used needles Avoid removing used needles from disposable syringes by hand Avoid bending, breaking, or manipulating used needles by hand Place used sharp objects and needles in puncture-resistant containers</td>
</tr>
</tbody>
</table>

*Table adapted from the Guidelines for Isolation Precautions in Hospitals from the HICPAC.\textsuperscript{177} Also available online at http://www.cdc.gov/ncidod/hip/isolat/isolat.htm.

### Standard Precautions

The key role of HCWs hands in the transmission of pathogens from patient to patient was demonstrated > 150 years ago by Ignaz Semmelweis. This obstetrician from Vienna was able to dramatically reduce the mortality related to puerperal fever by implementing systematic hand disinfection in chlorinated lime before examining patients.\textsuperscript{171} Since then, routine hand washing before and after patient contact remains the most important infection control measure.\textsuperscript{172,173}

The endemic transmission of exogenous staphylococci and other potential pathogens by the hands of HCWs is well-documented.\textsuperscript{91,94–97} This phenomenon is of particular concern in the ICU where patient care necessitates frequent contact. Goldmann et al\textsuperscript{98} reported the presence of Gram-negative bacilli on the hands of 75% of neonatal ICU personnel. As already mentioned, data have shown that one third to two thirds of the hands of HCWs in ICUs were found to be colonized by Candida spp.\textsuperscript{99} We have demonstrated\textsuperscript{174} that bacterial contamination of the hands increases linearly with time on ungloved hands during patient care (16 colony-forming units [CFU] per minute; 95% CI, 11 to 25 CFU/min). Higher contamination was documented with direct patient contact such as respiratory care, handling of body fluid secretions, and interruption in the sequence of patient care (ie, the HCW left the patient’s bedside to accomplish another task such as answering a telephone and then returned to resume care). We found that the method of hand cleansing before care affected the amount of bacterial contamination; in particular, the absence of hand disinfection before patient care was associated with an increase of 68 CFU (increase, 16 to 119 CFU), independent of the type of care provided and the hospital location.\textsuperscript{174} Updated guidelines for hand washing and/or hand disinfection were published by the Healthcare Infection Control Practices Advisory Committee (HICPAC)\textsuperscript{175} in 1995 (http://www.cdc.gov/ncidod/hip/sterile/sterile.htm). However, low-level compliance with hand hygiene has been systematically reported, particularly in ICUs where it does not exceed 40%.\textsuperscript{118,176–178} Several reasons have been suggested for such a low level of compliance, including the lack of priority over other required procedures, insufficient time, inconvenient placement of hand-washing facilities, allergy or intolerance to hand-hygiene solutions, and lack of leadership from senior medical staff.\textsuperscript{177,179–181} We have reported\textsuperscript{174} that compliance was inversely proportional to the number of opportunities per hour of patient care. In addition, those HCWs who do wash frequently and vigorously risk skin damage, which, ironically, results in the shedding of more organisms into the environment.\textsuperscript{182} Attempts to improve compliance with hand hygiene have been associated with some improvement.\textsuperscript{43,183} Only a few interventions have been associated with a sustained effect.\textsuperscript{25,184–186} The main parameters associated with successful improvement have been extensively discussed elsewhere (http://infection.thelancet.com), and examples based on published interventions are given herein.

Experience reported\textsuperscript{187} with alcohol-based handrubs suggested that hand disinfection reduces hand contamination more than hand washing. In a study published by Doebbeling et al,\textsuperscript{43} a hand-disinfection system using an antimicrobial agent (chlorhexidine) reduced the rate of NIs more effectively than one
using alcohol and soap. This improvement was essentially explained by a better compliance with hand-hygiene instructions when chlorhexidine was used.43 We observed that the promotion of hand disinfection with an alcohol-based hand-rub solution, which was distributed widely as disposable individual pocket bottles as well as placed at the patient bedside, may significantly improve the compliance of ICU staff for

Table 10—Requirements According to Transmission-Based Precautions*

<table>
<thead>
<tr>
<th>Precautions</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard precautions</td>
<td>Measles</td>
</tr>
<tr>
<td>Use standard precautions for the care of all patients</td>
<td>Varicella (including disseminated zoster)‡</td>
</tr>
<tr>
<td>In addition, use the following precautions</td>
<td>Tuberculosis§</td>
</tr>
<tr>
<td>Airborne precautions</td>
<td>Ebola, Lassa, Crimee-Congo, and Marburg</td>
</tr>
<tr>
<td>For patients known or suspected to have illnesses transmitted by airborne droplet nuclei</td>
<td>Neisseria meningitidis</td>
</tr>
<tr>
<td>Viral hemorrhagic fever</td>
<td>H influenzae</td>
</tr>
<tr>
<td>Droplet precautions</td>
<td>Diphtheria (pharyngeal)</td>
</tr>
<tr>
<td>For patients known or suspected to have illnesses transmitted by large particle droplets</td>
<td>M pneumoniae</td>
</tr>
<tr>
<td>Meningitis, pneumonia, epiglottitis, and sepsis</td>
<td>Pertussis</td>
</tr>
<tr>
<td>Other respiratory infections spread by droplet</td>
<td>Pneumonic plague</td>
</tr>
<tr>
<td></td>
<td>Streptococcal (group A) infections</td>
</tr>
<tr>
<td>Serious viral infections spread by droplet</td>
<td>Adenovirus‡</td>
</tr>
<tr>
<td></td>
<td>Influenza</td>
</tr>
<tr>
<td></td>
<td>Mumps</td>
</tr>
<tr>
<td></td>
<td>Parvovirus B19</td>
</tr>
<tr>
<td></td>
<td>Rubella</td>
</tr>
<tr>
<td>Contact precautions</td>
<td>MRSA</td>
</tr>
<tr>
<td>Patients known or suspected to have illnesses easily transmitted by direct patient contact or by contact with items in the patient’s environment</td>
<td>VRE</td>
</tr>
<tr>
<td>Infection/colonization with resistant bacteria¶</td>
<td>ESBL</td>
</tr>
<tr>
<td></td>
<td>Multiresistant F aeruginosa</td>
</tr>
<tr>
<td></td>
<td>Multiresistant E cloacae</td>
</tr>
<tr>
<td></td>
<td>C difficile</td>
</tr>
<tr>
<td>Enteric infections#</td>
<td>E coli O157:H7, Shigella, hepatitis A, rotavirus</td>
</tr>
<tr>
<td>Respiratory infections in infants/young children</td>
<td>Syncytial virus</td>
</tr>
<tr>
<td>Enteroviral infections in infants/young children</td>
<td>Rotavirus</td>
</tr>
<tr>
<td>Skin infections that are highly contagious</td>
<td>Parainfluenza virus</td>
</tr>
<tr>
<td></td>
<td>Diphtheria (cutaneous)</td>
</tr>
<tr>
<td></td>
<td>Herpes simplex virus (neonatal or mucocutaneous)</td>
</tr>
<tr>
<td></td>
<td>Impetigo</td>
</tr>
<tr>
<td></td>
<td>Noncovered abscesses, cellulitis, or decubitus</td>
</tr>
<tr>
<td></td>
<td>Pediculosis</td>
</tr>
<tr>
<td></td>
<td>Scabies</td>
</tr>
<tr>
<td></td>
<td>Staphylococcal furunculosis in infants and young children</td>
</tr>
<tr>
<td></td>
<td>Zoster (disseminated or in immuno compromised host)¶</td>
</tr>
<tr>
<td>Viral/hemorrhagic conjunctivitis</td>
<td>Ebola, Lassa, and Marburg</td>
</tr>
</tbody>
</table>

*Adapted from the Guidelines for Isolation Precautions in Hospitals from the HICPAC.177 Also available online at http://www.cdc.gov/ncidod/hip/isolat/isolat.htm. Most common examples are listed, but the list is not exhaustive.
†See Table 9.
‡Certain infections require more than one type of precaution.
§See reference 201.
¶Pharyngitis, pneumonia, or scarlet fever in infants and young children.
#GI, respiratory, skin, or wound infections or colonization with multdrug-resistant bacteria considered by the infection control program to be of special clinical and epidemiologic significance.
¶For all patients in case of C difficile, or diapered or incontinent patients in other cases.

CHEST / 120/6 / DECEMBER, 2001 2071
whom almost two thirds of their work time theoretically could be required for optimal adherence to infection control guidelines on hand hygiene practice.\textsuperscript{188} This was also the case in a French medical ICU\textsuperscript{178} where the increase in compliance to hand hygiene measures from 42.4 to 60.9\% was essentially attributed to the availability of an alcohol solution for handrubs. However, the effect of this punctual intervention was not sustained, and compliance decreased over a 3-month period from 60.9 to 51.3\%. At our institution, the promotion of an elementary bedside hand-disinfection technique by a hospital-wide campaign resulted in a sustained improvement in compliance with hand hygiene from 48 to 66\% over 4 years. During the same period, the prevalence of overall NIs and MRSA transmission decreased from 16.9 to 9.9\% and from 2.16 to 0.93 episodes per 10,000 patient-days, respectively. Considering the hypothesis that only 25\% of the reduction in the infection rates could be attributed to the improved compliance in hand hygiene practice, this intervention might have prevented >900 NIs and, thus, was largely cost-effective.\textsuperscript{25} Behavioral changes may have played a key role in the success of this intervention, based on a multimodal and multidisciplinary approach including communication and education tools such as “Talking Walls” (widely exhibited cartoon posters, which are available at www.hopisafe.ch), active participation and positive feedback at both the individual and institutional levels, and the systematic involvement of institutional leaders.\textsuperscript{185,189−191}

Other requirements for standard precautions are listed in Table 9. Gloves should be used for any anticipated contact with blood, mucous membranes, nonintact skin, secretions, and moist body substances of all patients.\textsuperscript{192} However, gloves may have small and/or inapparent defects or may be torn during use so that hands may become contaminated.\textsuperscript{193−196} Doebbeling et al\textsuperscript{197} showed not only that washing gloved hands was ineffective for decontamination but, also, that 5 to 10\% of hands were contaminated after glove removal. This explains why the gloves themselves may be potentially responsible for the unrecognized cross-transmission of pathogens if they are not changed between patient contacts and if hands are not scrupulously washed or disinfected before and after degloving.\textsuperscript{198,199} In addition to gloves and gowns, masks must be used to protect mucous membranes of the eyes, nose, and mouth during procedures and patient-care activities that are likely to generate splashes or sprays of blood, body fluid secretions, and excretions.\textsuperscript{164} The simultaneous use of goggles or a mask that includes a transparent eyeshade are strongly recommended for the respiratory care of patients receiving mechanical ventilation (e.g., mouth care, suction or aspiration in the endotracheal tube, or aerosol therapy).

### Transmission-Based Precautions

In addition to standard precautions, transmission-based precautions include specific measures according to the mode of transmission of the microorganisms. Although all theoretical requirements for an ideal isolation system would be practically unfeasible, appropriate isolation remains the cornerstone of infection control measures to prevent the transmission of microorganisms from and/or to the patients. Recommendations for patient placement, including isolation in special rooms, are included in the requirements for transmission-based precautions (Tables 10 and 11).\textsuperscript{164,170,200} Source isolation would prevent the transmission of microorganisms from the patient.

**Airborne Precaution:** In addition to standard precautions, airborne precautions prevent the transmission of microorganisms transmitted by the inhalation of droplet nuclei or contaminated dust particles. Droplet nuclei are <5 \(\mu\)m in size and can remain

<table>
<thead>
<tr>
<th>Patient Care or Action Planned</th>
<th>Gloves</th>
<th>Gown</th>
<th>Mask</th>
<th>Eye Protection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protection against contact-transmitted pathogens</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Protection against droplet-transmitted pathogens</td>
<td>No</td>
<td>No</td>
<td>Yes†</td>
<td>Yes</td>
</tr>
<tr>
<td>Protection against airborne-transmitted pathogens</td>
<td>No</td>
<td>No</td>
<td>Yes‡</td>
<td>No</td>
</tr>
<tr>
<td>Anticipated contact with any body fluid§</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>For venipunctures and all invasive procedures</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>For any contact with mucous membrane or with nonintact skin</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>During all patient-care activities likely to generate splash or spray of any body fluid§</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes‡</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*Table adapted from HICPAC guidelines.\textsuperscript{164,200}
†Surgical masks are sufficient.
‡N-95 standard certified-mask 170.
§Blood, bloody or non-bloody body fluids, excretions, and secretions, except for sweat.
suspended in the air for long periods and can travel long distances. This is the case for patients with pulmonary and laryngeal tuberculosis, varicella and disseminated zoster, acute viral hemorrhagic fever, or measles, who should be placed in a private room with negative air pressure in relation to the surrounding area with at least six air changes per hour and with an appropriate discharge of air before it is circulated to other areas in the hospital.201 The door of the room should be kept closed. An isolation room with an anteroom is sometimes used, however, it is unknown whether the anteroom adds to the effectiveness of the isolation. The main role of the anteroom is to allow air pressure differentials to be maintained at the time of door opening. When an isolation room with an anteroom is used, the two doors should not be opened at the same time. In addition, the efficacy of such engineering controls applied to the air pressure has to be monitored. Inappropriate outward airflow was observed in 38% of 140 respiratory isolation rooms in the state of New York from 1992 to 1998. Multiple factors were identified as being associated with the malfunction of these sophisticated rooms, including an unbalanced ventilation system, a shared anteroom, a turbulent airflow pattern, and automated control system inaccuracies. All the factors were detected by a simple visible smoke test, which should be included in the list of controls in the charge of infection control team.202 Specifications for the ventilation of the room, such as negative pressure with external extraction of the contaminated air after adequate filtration for the patients infected or colonized by airborne-transmitted agents.203 When such isolation rooms are unavailable, the patient should be placed in a private room or placed in a cohort with another patient infected by the same organism. In these situations, however, a consultation with the infection control team is advised. Airborne precautions require respiratory protection for any HCWs or visitors with high-efficiency masks (dust masks) that have been approved by the National Institute for Occupational Safety and Health (N-95 standard).170,203 This also has to be applied to the patient during transport and/or movements outside his isolation room.

**Droplet Precaution:** In addition to the standard precautions, droplet precautions prevent the transmission of microorganisms transmitted by large particles (ie, those particles > 5 μm in size) containing infecting microorganisms that are produced during coughing, sneezing, and talking, or during invasive procedures such as bronchoscopy and suctioning. They can also be deposited on the mucous membranes of the host’s eyes, nose, and mouth. This is the case for *Haemophilus influenzae* type B, meningococci, multidrug-resistant pneumococci or any other multidrug-resistant organisms in the respiratory tract (eg, MRSA, ESBLs, or Gram-negative bacteria), pharyngeal diphtheria, *Mycoplasma pneumoniae*, and some viral diseases (Table 10). However, a close contact of < 60 cm to 1 m is necessary for transmission to occur since respiratory droplets do not last very long in the air and usually travel short distances. In addition to the standard precautions, a mask is recommended when an HCW is working within 60 cm to 1 m of the patient. Droplet precautions require the patient to be placed in a private room or to be placed in a room with another patient infected by the same organism. Special air handling and ventilation are unnecessary, and the door may remain open. When these measures are not possible, a spatial separation of at least 60 cm to 1 m between the patient and other patients or visitors should be observed.

**Contact Precaution:** In addition to standard precautions, contact precautions prevent the transmission of epidemiologically important microorganisms (ie, MRSA, ESBLs, Gram-negative bacteria, VRE, or *Clostridium difficile*) that can be transmitted by physical direct or indirect contact with the patient or his direct environment. The patient is to be placed in a private room or in a room with another patient infected by the same organism. For any contact with the patient, HCWs should wear gloves and gowns, which should be removed before leaving the room, and this should be followed by systematic hand disinfection measures. Patient-care devices, including stethoscopes and blood-pressure cuffs, should not be used for other patients without rigorous cleansing and disinfection.

Protective isolation measures for immunosuppressed patients such as those who have undergone transplantation or who are deeply neutropenic, have been published.201,203,204 In addition to standard precautions, they include contact precautions as well as the placement of the patient in a private room with filtered air instilled in positive pressure.201,203,204

Private rooms with specific ventilation specifications probably could improve the efficacy of airborne droplet and contact precautions, but that kind of specification is particularly difficult to obtain in most ICUs. In addition, some authors205–207 have pointed out that, apart from the practical difficulties involved in introducing this isolation measure, additional difficulties also may be associated with some psychological stress that has also to be taken into account.205–207 However, because aggressive support for organ failure in a critically ill patient must be
considered as an absolute priority, isolation precautions often are imposed as secondary management objectives.

Patients who are readmitted to the hospital are at particularly high risk for carrying and transmitting resistant microorganisms that were acquired during a prior hospitalization. Those with suspected infections should be appropriately segregated at the time of hospital admission. When a private room is not available, patients infected or colonized by the same microorganism can share a room. This situation, which is referred to as cohorting, can be safely used provided that the patients are not infected with other potentially transmissible pathogens and that the likelihood of reinfection with the same microorganism is minimal.

**Control of Antimicrobial Use**

As previously discussed, the use of antimicrobial agents has been shown to be one of the major determinants in the shift toward resistant strains.\(^{207}\) Accordingly, most experts in infectious diseases and infection control now recommend a strict limitation of antibiotic use.\(^{208,209}\) Several strategies targeted at the use of antimicrobial agents have been suggested to control the emergence of resistance. They include the following: an optimal use of antimicrobial agents; strict control, removal, or restriction of the agents; use of antimicrobial agents in combination; and cycling of the available agents.\(^{210}\)

Antimicrobial use can be divided into the following three categories: definite therapy for proven infections; prophylaxis for specific infections; and empirical therapy for suspicion of infection (with the latter representing the large majority of cases). Considering the high mortality and morbidity associated with NIs, most intensivists systematically apply the concept of early empirical broad-spectrum antimicrobial coverage for critically ill patients in whom the development of an NI is suspected.\(^{208}\)

The selection of antimicrobial agents to be prescribed to critically ill patients is crucial. In a surveillance study of 2,000 consecutive ICU patients, Kollef et al\(^ {22}\) evaluated the treatment administered to 655 patients with either community-acquired infections or NIs. Inadequate antimicrobial treatment was prescribed in 45% of patients with NIs that developed following therapy for a community-acquired infection, in 34% of patients with NIs alone, and in 17% of patients with community-acquired infections \((p < 0.0001).\) The mortality rate of patients receiving inadequate therapy \((52%)\) was significantly higher than that for those receiving adequate treatment \((12%)\) \((\text{adjusted OR}, 4.26; 95\% \text{ CI}, 3.52 \text{ to } 5.15; \ p < 0.001).\) Prior administration of antibiotics \((\text{adjusted OR}, 3.39; 95\% \text{ CI}, 2.88 \text{ to } 4.23; \ p < 0.001),\) the presence of bloodstream infection \((\text{adjusted OR}, 1.88; 95\% \text{ CI}, 1.52 \text{ to } 3.32; \ p = 0.003),\) an increasing APACHE II score \((\text{adjusted OR}, 1.04; 95\% \text{ CI}, 1.03 \text{ to } 1.05; \ p = 0.002),\) and decreasing patient age \((\text{adjusted OR}, 1.01; 95\% \text{ CI}, 1.01 \text{ to } 1.02; \ p = 0.012)\) were independently associated with inadequate antimicrobial prescriptions.\(^{22}\) These data confirmed previous observations made in both critically ill and neutropenic cancer patients.\(^ {211–218}\)

This conflict of interest is responsible for a vicious circle in which microorganisms could potentially emerge as the true winners and has stimulated the development of new strategies targeted at a better use of antimicrobial agents.\(^ {219}\) Guidelines for the systematic evaluation of fever in critically ill patients have been developed.\(^ {220,221}\) They facilitate the early recognition of NIs, which must be based on a high index of suspicion. Additional guidelines\(^ {222–225}\) for the administration of empirical antimicrobial therapy may help in choosing appropriate agents. The implementation of such general recommendations in both surgical and medical ICUs has been reported to reduce costs without adversely affecting patients’ outcomes.\(^ {36,45,226}\) Methods for an optimal coverage of pathogens that may be potentially resistant to empirical antimicrobial therapy would include the selection of a new class of antimicrobial agents or the routine administration of combined agents from different classes. It should be mentioned that the efficacy of a combination of aminoglycoside with \(\beta\)-lactam remains controversial. Based on an \textit{in vitro} synergistic effect, its clinical utility was demonstrated only for tuberculosis and HIV infections. In addition, most new-generation agents already cover a very broad spectrum. Accordingly, most experts do not systematically recommend such combinations as initial empirical therapy for any suspected infections.\(^ {214,220,227–231}\)

Any empirical treatment has to be reevaluated after 48 to 72 h. By taking into account the results of the initial cultures and the clinical evolution, the spectrum can usually be narrowed without compromising patient outcome. This strategy was recently applied to the management of ventilator-associated pneumonia by Fagon et al.\(^ {20}\) They compared noninvasive vs invasive diagnostic techniques as standard management in a series of 413 consecutive patients suspected of developing such a complication. The invasive workup consisted of bronchoscopy with direct examination, and empirical therapy was started if results of testing were positive. Further treatment was started, adjusted, or discontinued according to the results of quantitative cultures obtained from protected-brush specimens or BAL fluid. The invasive approach resulted in the treat-
ment of 52% of patients (107 of 204 patients) with antibiotics (44% of patients [90 of 204 patients] did not receive antibiotics), compared with the noninvasive approach in which 91% of patients (191 of 209 patients) were treated with antibiotics (7% of patients [18 of 209 patients] did not receive antibiotics). In addition, the former strategy was associated with a significant reduction in the number of antibiotic-free days at day 7 (2.2 vs 5.0, respectively; \( p < 0.001 \)) and at day 28 (7.5 vs 11.5, respectively; \( p < 0.001 \)). Furthermore, the mortality rate was markedly reduced at day 14 (26% vs 16%, respectively; \( p = 0.022 \)). This invasive diagnostic strategy may become the standard of care for diagnosing ventilator-associated pneumonia and should be considered as part of an antibiotic control strategy in the ICU.\textsuperscript{232} This may also contribute to limiting the selective pressure of antimicrobial agents on ward microorganisms.

The inappropriate use of antibiotics, related to either too generous or too restrictive use, has stimulated the application of computerized antimicrobial guidelines. Automatic stop orders after 72 h of empirical use have been proposed, but the risk of an inadequate interruption of treatment is worrying.\textsuperscript{166} More sophisticated algorithms have been applied.\textsuperscript{233,234} The impact of a computerized decision-support program linked to computer-based patient records designed to assist physicians in the use of antimicrobial agents was evaluated by Evans et al\textsuperscript{226} over a 12-month period in a 12-bed ICU. Compared with the preceding 2-year period, there was a marked reduction in antibiotic prescriptions (67% vs 73%, respectively; \( p < 0.03 \)), in orders for drugs to which the patient had reported an allergy (6.4% vs 13%, respectively; \( p < 0.01 \)), in excess drug dosages (16% vs 36%, respectively, \( p < 0.01 \)), and in antibiotic-susceptibility mismatching (2.2% vs 18%, respectively; \( p < 0.01 \)). Moreover, compared with those who did not receive the proposed regimens and those in the preintervention cohort, patients who always received the recommended regimens had a significant reduction in the cost of antibiotics (adjusted means, $102 vs $427 and $340, respectively; \( p < 0.001 \)), in total hospital costs (adjusted means, $26,315 vs $46,865 and $35,283, respectively; \( p < 0.001 \)), in the length of ICU stay (adjusted means, 2.7 vs 8.3 and 4.9 days, respectively; \( p < 0.001 \)), and length of hospital stay (adjusted means, 10.0 vs 16.7 and 12.9 days, respectively; \( p < 0.001 \)). In addition to this reduction in costs and improvement of the quality of patient care, these data also suggested that with computerized algorithms, fewer patients are exposed to lower amounts of antibiotics.

The scheduled change of antibiotic classes, also called antimicrobial agent cycling, has been one of the strategies advocated to limit the trend of increasing antimicrobial resistance among nosocomial pathogens.\textsuperscript{210,219,235,236} Gerdng et al\textsuperscript{217} used a scheduled rotation of amikacin and gentamicin when a high level of resistance to the latter was reached among \( P \) aeruginosa isolates. The incidence of gentamicin resistance was reduced, and it could be further reintroduced for the treatment of severe infections. By restricting the use of cefotaxime, vancomycin, and clindamycin by the addition of \( \beta \)-lactam/\( \beta \)-lactamase inhibitors to replace third-generation cephalosporins after failure of the implementation of barrier precautions for VRE-infected patients, Quale et al\textsuperscript{134} observed that the rate of GI VRE-colonization was reduced from 47% to 15% of patients (\( p < 0.001 \)). The impact of a scheduled change from cefotaxime to ciprofloxacin that was prescribed as empirical treatment for septic patients after cardiac surgery was recently evaluated by Kollef et al\textsuperscript{46} for > 12 months. The incidence of ventilator-associated pneumonia (6.7% vs 12%, respectively; RR, 0.58; 95% CI, 0.35 to 0.95; \( p = 0.028 \)) and of ventilator-associated pneumonia attributed to antibiotic-resistant Gram-negative bacteria (0.9% vs 4.0%, respectively; RR, 0.23; 95% CI, 0.07 to 0.80; \( p = 0.013 \)) was significantly lower following the recommendations. Among 41 episodes of ventilator-associated pneumonia or bacteremia in the first period, 20 episodes (49%) were due to antibiotic-resistant Gram-negative bacteria, compared with 4 of 20 episodes (20%) during the second period (\( p = 0.05 \)). The use of postoperative antibiotics in addition to the perioperative prophylaxis was high, however, in both periods (45% vs 43% of patients, respectively; \( p = 0.605 \)), and no impact was shown on mortality rates. Nonetheless, these preliminary data are provocative and suggest that such a strategy could minimize the emergence of resistant microorganisms by reducing the selection pressure for bacteria to develop resistance to a specific antibiotic.\textsuperscript{238,239} Gruson et al\textsuperscript{240} reported a positive impact on the incidence of ventilator-associated pneumonia due to resistant Gram-negative bacteria over 4 years after the implementation of a strategy combining a rotation and a restriction of the use of antibiotics. The schedule for antibiotic therapy consisted of monthly rotations of the agents (ie, four different \( \beta \)-lactams combined with four different aminoglycosides) for the empirical treatment of pneumonia with a succession of cycles of 4-month periods over 2 years after its implementation. Gruson et al\textsuperscript{240} observed a decrease from 231 patients with ventilator-associated pneumonia in the prestudy period to 161 patients in the period following the study (\( p < 0.01 \)). The total number of potentially resistant Gram-
negative bacilli responsible for pneumonia decreased from 140 to 79, respectively. If such a strategy could be validated, this may become a highly cost-effective measure.241

However, these recommendations cannot replace a good knowledge of the local epidemiology and of the resistance profile of the prevailing in-hospital and out-of-hospital pathogens. A multidisciplinary approach, including the microbiology laboratory and experts in infectious disease and infection control, may be required for some difficult cases.

Selective Digestive Decontamination

Colonization is a prerequisite for the development of NIs that frequently arises from the endogenous flora in the oropharyngeal and GI tracts. Antimicrobial prophylaxis targeted at the elimination of these reservoirs has been the subject of very active clinical research during the past 2 decades.242 The aim of this elegant concept, called selective digestive decontamination (SDD), is to prevent the overgrowth of potentially pathogenic Gram-negative aerobic bacilli and yeasts by using oral, nonabsorbable antibiotics that preserve the endogenous anaerobic flora.243,244 In addition to its potential benefit in preventing ICU-acquired infections, SDD was initially thought to contribute to the reduction of endotoxemia from the bowel flora, which may play a role in the pathophysiology of multiple organ failure.245,246

After the initial enthusiasm related to positive results in reducing the rates of ventilator-associated pneumonia, randomized controlled studies247–251 showed that SDD was effective in selected groups of patients only. Meta-analysis showed conflicting results, possibly due to the effect of early-onset infections, which were not uniformly taken into account or treated in some studies.251–254 It was later demonstrated that SDD is only efficient after several days and that its effect can only be considered in patients with late-onset NIs, against which SDD is very effective.255–258 Nonetheless, many regimens did include vancomycin or aminoglycoside, and the emergence of resistant microorganisms possibly related to the introduction of SDD was observed in several centers.259–261 This selective pressure on the epidemiology of resistance definitely precludes the systematic use of SDD for critically ill patients. However, controlled studies confirmed that it may still have a place in carefully selected groups of high-risk patients in whom its efficacy and cost-effectiveness have been established251,262–265 (Table 12).

Infection Site and Specific Preventive Measures

Prevention of Ventilator-Associated Pneumonia

Research for effective measures to prevent ventilator-associated pneumonia have been recently reviewed elsewhere21,266–268 and is only briefly summarized below.

A large proportion of cases of ventilator-associated pneumonia are related to the continuous aspiration of contaminated oropharyngeal secretions and/or possibly to gastric content.247,249,270 The simplest measure with which to decrease the aspiration of gastric contents in mechanically ventilated patients is to place them in a semirecumbent position (ie, a 45° angle).271 Several randomized studies272 have found that sucralfate, which does not lower gastric pH, is associated with lower rates of ventilator-associated pneumonia than histamine H2-receptor antagonists, but some data273 suggest that it may be less efficient in stress ulcer prophylaxis, and this field continues to be controversial.274 As mentioned previously, SDD is effective in subsets of mechanically ventilated patients. The continuous subglottic aspiration of oropharyngeal secretions over the tracheal cuff is an original concept first developed by Valles et al.275 In a series of 190 mechanically ventilated patients, these authors observed a marked reduction in the incidence-density of nosocomial pneumonia from 39.6 episodes per 1,000 ventilator-days to 19.9 episodes per 1,000 ventilator-days in patients receiving continuous aspiration. These data have been confirmed by Kollef et al276 in patients after cardiac surgery.

Noninvasive ventilation was shown to significantly reduce the risk of nosocomial pneumonia.277,278 Antonelli et al279 reported that nosocomial pneumonia or sinusitis occurred in 1 of 32 critically ill patients (3.1%) who received ventilation with noninvasive techniques compared to 10 of 32 patients (32%) who received mechanical ventilation over a 12-month period (p = 0.003). Moreover, observations by Nourdine et al280 in a 20-bed multidisciplinary ICU

| Table 12—Possible Indications for SDD in ICU Patients |
|---------------|---------------------------------|
| Indications   | Measures                        |
| Prolonged (> 2 weeks) neutropenia* | Prolonged ICU stay (> 5 d)† |
| Multiple trauma |                                |
| Mechanical ventilation |                                |
| Outbreak of multiresistant Gram-negative bacilli |                                |
| Solid-organ transplant recipients |                                |

*Supported by a meta-analysis. †Not supported by evidence-based evaluation.

2076 Critical Care Reviews
over a 27-month period suggested that noninvasive ventilation also may have a positive impact on other NIs. The incidence-density of lower respiratory tract, urinary tract, and bloodstream infections was 14.2 episodes per 1,000 patient-days in 129 patients who had undergone successful noninvasive ventilation, compared with 30.3 episodes per 1,000 patient-days in those patients (607 patients) who required mechanical ventilation. This was also probably related not only to less continuous sedation but also to the use of fewer invasive devices such as central venous access and urinary catheterization.

Nosocomial Sinusitis

Although frequently related to pathogens that are endemic in the hospital, including anaerobes, nosocomial sinusitis is not included in the published data from the NNIS system and is only rarely reported in studies on the epidemiology of NIs in critically ill patients. Cumulative incidence rates between 38.5% and 100% have been reported from prospective observational studies in critically ill patients, and it was suggested that these infections may be responsible for a large proportion of sepsis without other documented foci of infection. However, nonspecific symptoms, especially in critically ill, sedated patients in whom pain and purulent discharge may be unrecognized, as well as the absence of uniform criteria may explain this wide range. More restrictive criteria combining the presence of both purulent secretions and radiologic involvement lead to lower estimates of the incidence of nosocomial sinusitis, which is reported as ranging between 5% and 35%.

In the early 1970s, retrospective studies strongly suggested that they may be ventilator-associated. Their pathophysiology, elucidated in the 1980s, includes impaired drainage of the sinus cavities in the supine position, slowed venous drainage due to positive-pressure ventilation, and obstructive devices such as nasogastric or nasotracheal tubes. The increased risk of infection due to the presence of a nasal device was confirmed in several trials. In a prospective observational cohort study of 366 patients in two medical ICUs over 1 year, the incidence of nosocomial sinusitis, which was defined as radiographic abnormalities in one or both maxillary sinuses with recovery of microorganisms from cultures obtained by transnasal aspiration, was 7.7% with an incidence rate of 12 cases per 1,000 patient-days (95% CI, 8.3 to 17.3). These rates were 15.7 cases per 1,000 patient-days (95% CI, 10.8 to 22.9) for patients with a nasoenteric tube, whether they received mechanical ventilation or not, and 1.6 cases per 1,000 patient-days (95% CI, 0.3 to 9.1) for those patients without a nasal device. In patients who were receiving mechanical ventilation through orotracheal tubes, the incidence was 19.8 episodes per 1,000 nasoenteric tube-days (95% CI, 13.6 to 28.8). Risk factors identified by multiple logistic regression analysis were as follows: nasal colonization with enteric Gram-negative bacilli (OR, 6.4; 95% CI, 2.2 to 18.8; p = 0.0007); feeding via nasoenteric tube (OR, 14.1; 95% CI, 1.7 to 118; p = 0.015); sedative use (OR, 15.9; 95% CI, 1.9 to 134; p = 0.011); and Glasgow coma scale of < 8 (OR, 9.1; 95% CI, 3.0 to 27.3; p = 0.0001).

In 1994, Rouby et al evaluated 162 consecutive patients who had received ventilation for > 1 week, with paranasal CT scans performed within 48 h of hospital admission and 7 days later. The patients were stratified according to the initial radiologic aspect of their maxillary sinuses (normal, 40 patients; mucosal thickening, 26 patients; and radiologic sinusitis defined as the presence of either an air fluid level or total opacification, 96 patients). The patients without sinusitis were randomized either to nasotracheal or orotracheal intubation, and they underwent further imaging studies 7 days later. Radiologic sinusitis developed in 95% of patients with a nasal tube compared to 22.5% of those with an oral tube (p < 0.001). After 7 days, 46% of the patients with mucosal thickening developed radiologic sinusitis and 12% normalized. In the group of patients with initial radiologic sinusitis, a stepwise logistic regression analysis identified nasotracheal tube (p < 0.001), nasal gastric tube (p < 0.05), duration of endotracheal intubation (p < 0.01), and duration of gastric tube placement (p < 0.05) to be independent risk factors. The sinusitis could be microbiologically confirmed by a transnasal puncture in only 51 of 133 patients (38%) who had a radiologic involvement. Despite the fact that > 80% of patients had radiologic involvement of the ethmoid and sphenoid sinuses, the drainage of the maxillary sinuses with only lavages twice daily (ie, 5 mL saline solution with 50 mg amikacin) without systemic antibiotic therapy was associated with an improvement of sepsis in 49% of patients, 67% of whom had microbiologically documented sinusitis. Among patients with initial radiologic sinusitis, ventilator-associated pneumonia developed in 67% in whom sinusitis was microbiologically documented after 7 days, compared to 43% in the rest of the group (p < 0.02). These elegant studies confirmed that foreign devices in the nose represent a major risk factor for the development of nosocomial sinusitis, which itself is a risk factor for the development of pneumonia. More importantly, it also suggests that although a definite diagnostic regimen should include a transnasal punct-
ture, drainage and lavage for > 15 days without systemic antibiotic therapy may also be useful in the management of ventilated patients with sepsis of unknown origin in the presence of radiologically documented sinusitis.

In a study from France, Holzapfel et al. evaluated the impact of a systematic search and treatment of maxillary sinusitis in 399 patients who had received mechanical ventilation through a nasotracheal tube on the occurrence of ventilator-associated pneumonia. In the intervention group, sinusitis, defined as a temperature of ≥ 38°C with radiologic signs evident on a CT scan in the presence of purulent transnasal aspirate of the involved sinus, was diagnosed in 80 of 199 patients and was treated by lavage and systemic antibiotic therapy. In the control group, no patient was treated for sinusitis. Ventilator-associated pneumonia then was observed in 37 patients (34%) in the study group and in 51 patients (47%) in the control group (RR, 0.71; 95% CI, 0.40 to 0.92; p = 0.02). Overall, the 60-day mortality rate was further estimated at 36% in the study group and 46% in the control group (RR, 0.71; 95% CI, 0.52 to 0.97; p = 0.03).

In summary, nosocomial sinusitis is probably underestimated in critically ill patients who are receiving mechanical ventilation, in whom it may be viewed as a direct consequence of impaired drainage capability of the sinus cavities due to devices placed in the nose. This represents a significant risk factor for the development of further nosocomial pneumonia. Its prevention would include the avoidance of nasotracheal intubation and the systematic use of the orotracheal route, which is the current practice in many ICUs. Scrupulous oral hygiene for patients receiving mechanical ventilation is mandatory. Nasotracheal feeding tubes should theoretically also be avoided, but this is practically difficult in non-sedated patients.

Bloodstream Infections and Specific Preventive Measures

A large proportion of catheter-related infections are preventable through careful control of the factors associated with their colonization by microorganisms. For example, the insertion site of the catheter was demonstrated to be an important risk factor and is potentially easily influenced by clinical practice. Growing evidence has suggested repeatedly that central lines inserted into the jugular site are more likely to be colonized than those lines inserted by the subclavian route. This could be related to factors favoring skin colonization such as proximity of oropharyngeal secretions, higher skin temperature, and difficulties in immobilizing the catheter and maintaining an optimal dressing, particularly in men. Although infection rates for CVCs inserted through the femoral vein have not been reported to be higher since the beginning of the 1990s, despite potentially less severe complications related to their insertion, they may be associated with a higher rate of deep venous thrombosis. At present, insufficient data are available to recommend their systematic use.

The use of a tunneled short-term CVC has been reported to be associated with a decreasing rate of device-related infection, and a meta-analysis of randomized controlled trials concluded that it may be the case only for those CVCs inserted into the jugular site. An accompanying editorial highlighted the fact that blood drawn through the catheter was not allowed in the largest study included in the meta-analysis, a factor that might have contributed to the low reported rate of infection. The same comment has to be made about a more recent large randomized controlled study in which the authors reported that catheter-related sepsis occurred in 5 of 168 patients (3.0%) who had received femoral tunneled CVCs compared with 15 of 168 patients (8.9%) who had received nontunneled CVCs (RR, 0.25; 95% CI, 0.09 to 0.72). The proportion of CVCs used for drawing blood is generally not specified in most studies, and many institutions favor arterial lines for this purpose.

Prospective, randomized clinical studies have shown that the use of CVCs impregnated on their external surface with chlorhexidine-silver-sulfadiazine were associated with a marked reduction of microbiologically documented, catheter-related infections. A meta-analysis of 2,611 catheters from 12 studies found that these catheters were associated with a reduction of colonization (OR, 0.44; 95% CI, 0.36 to 0.54; p < 0.001) and catheter-related bloodstream infection rates (OR, 0.56; 95% CI, 0.37 to 0.84; p = 0.05). A cost-effectiveness analysis based on these results suggested that a decreased incidence of catheter-related bloodstream infections of 3.4 to 1.2% corresponded to a cost savings of $68 to $391 per catheter used. Catheters impregnated with minocycline and rifampin on both the external surface and the intraluminal face also were associated with a reduction of microbiologically documented, catheter-related infections. These new materials have been compared in a multicenter study. The minocycline/rifampin-impregnated catheter was reported to be associated with significantly lower levels of colonization (RR, 0.35; 95% CI, 0.24 to 0.55) and catheter-related bloodstream infection (RR, 0.85; 95% CI, 0.01 to 0.63). The authors argue that this difference may be due, in part, to the lack of
antibacterial activity on the intraluminal surface. This is consistent with the results of another study\(^{311}\) in which the silver/chlorhexidine catheters were not associated with a reduction of the catheter-related infection rates. Recent data on the determination of colonization and residual antimicrobial ex vivo activity after removal of 113 CVCs that were no longer required, strongly favors this hypothesis.\(^{312}\) It has been suggested that the potential cost-benefit could be sufficiently high to favor the use of these second-generation catheters in ICUs.\(^{298,313}\) However, the duration of catheterization may have played a role. Impregnated catheters failed to prevent catheter-related infections in only one study, which included neutropenic cancer patients with a mean duration of catheterization of 20 days\(^{311}\) compared to 6,\(^{298}\) 7,\(^{305}\) and 8,\(^{310}\) days in other reports. This may be confirmed by our data from a meta-analysis\(^{314}\) of 20 studies including 3,981 catheters that showed that the maximum benefit of coating was achieved during the first week of catheterization (relative benefit, 0.35; 95% CI, 0.18 to 0.67) and that no additional benefit was apparent beyond 2 weeks of use. Despite these impressive results, these devices may be potentially associated with the emergence of resistance, and their eventual place in the care of patients remains to be determined.\(^{139,315}\)

Other preventive approaches, based on the implementation of locally adapted practice guidelines to take into account careful indication and choice of the type of vascular access, rigorous insertion practice, and optimal catheter care with regular surveillance programs, have been developed (Table 13).\(^{296,316,317}\) We recently reported\(^{34}\) the impact of a global strategy targeted at the reduction of catheter-related infections in 3,154 critically ill patients who had been consecutively admitted to our medical ICU. The results revealed a decrease in the incidence of nosocomial bloodstream infections by 67% (RR, 0.33; 95% CI, 0.20 to 0.56; \(p < 0.001\)), corresponding to a decrease from 6.6 to 2.3 episodes per 1,000 CVC-days and a 64% decrease in exit-site catheter infections (RR, 0.36; 95% CI, 0.20 to 0.63; \(p < 0.001\)). Importantly, the overall incidence of ICU-acquired infections was reduced by 35% (RR, 0.65; 95% CI, 0.54 to 0.78; \(p < 0.001\)). Our prevention strategy may have prevented > 75 NIs during the 8 months of the intervention, including at least 30 primary bloodstream and 25 vascular-access infections. Using conservative estimates of the attributable costs associated with the latter two types of infections when transferred to the Swiss health-care setting, the program was largely beneficial for the patient and the hospital.\(^{73,318}\) The prevention of those infections would amount, at least, to the annual salary of three full-time infection-control nurses.

Table 13—Specific Recommendations for the Prevention of Catheter-Related Infections

<table>
<thead>
<tr>
<th>Type of Action</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Material preparation</td>
<td>Material has to be prepared according to a detailed list (hospital policy) to avoid interruption during insertion</td>
</tr>
<tr>
<td>Patient installation</td>
<td>Precise recommendations for the placing of patients and devices to guarantee optimal access to the insertion site. The presence of a nurse to assist the physician is strongly recommended.</td>
</tr>
<tr>
<td>Insertion</td>
<td>Specific training for ICU physicians and detailed written guidelines for the staff are recommended.(^{24,319})</td>
</tr>
<tr>
<td>Skin preparation</td>
<td>Hair-cutting instead of shaving; skin cleansing with surgical swab</td>
</tr>
<tr>
<td>Skin antisepsis</td>
<td>Alcohol-based (70%) solution with chlorhexidine gluconate (0.5%), with 2-min drying time before insertion</td>
</tr>
<tr>
<td>Barrier precautions</td>
<td>Maximal sterile barriers; sterile gown, gloves and large drapes; cap, surgical mask</td>
</tr>
<tr>
<td>Insertion technique</td>
<td>Consider systematic promotion of subclavian site for CVCs and wrist vein for short lines</td>
</tr>
<tr>
<td>Dressing</td>
<td>Discard occlusive devices and promote dry gauze-based dressing occluded with porous adhesive band</td>
</tr>
<tr>
<td>Replacement</td>
<td>Any vascular access: prompt removal if indicated, no routine replacement</td>
</tr>
<tr>
<td>General handling</td>
<td>Administration sets and devices: replacement at 72-h intervals</td>
</tr>
<tr>
<td></td>
<td>Lines for lipid emulsion: replacement at 24-h intervals</td>
</tr>
<tr>
<td></td>
<td>Lines for blood product: remove these lines immediately after use</td>
</tr>
<tr>
<td>Device removal</td>
<td>Peripheral line: remove them after 72 h systematically</td>
</tr>
<tr>
<td></td>
<td>Central line: remove them as clinically indicated, no routine replacement</td>
</tr>
<tr>
<td></td>
<td>Any vascular access: prompt removal if not absolutely necessary</td>
</tr>
<tr>
<td>Hand hygiene</td>
<td>Clinical sepsis: guidewire exchange if unexplained by another potential source of infection</td>
</tr>
<tr>
<td>Hand hygiene</td>
<td>Systematic application of the requirements of standard precautions (Table 9)</td>
</tr>
</tbody>
</table>

\(^{*}\)Table adapted from references 24 and 296. \(^{†}\)For the insertion of all but peripheral lines.\(^{317}\)

Sherertz et al\(^{319}\) recently reported that an educational program for physicians in training also can decrease the risk of catheter-related infection. A 1-day course on infection control practice and on procedures targeted at vascular access insertion was
shown to reduce the rate of catheter-related infections by 27%, from 3.3 to 2.4 per 1,000 CVC-days.319 Importantly, the impact obtained from the reduction of NIs in these two studies308,309 was largely superior to that expected with the use of antimicrobial/antisepsis-coated catheters. Behavioral changes may have played a key role in the success of these interventions.

**UTIs**

Nosocomial UTIs are almost exclusively related to urinary catheters or invasive urinary tract procedures. Sixty-nine percent of the 181,993 patients hospitalized in 112 medical ICUs in NNIS hospitals from 1992 through 1997 had urinary catheters.35 This proportion ranged from 32% in pediatric ICUs, to 44% in coronary-care units, and to > 80% in cardiothoracic and trauma ICUs.45,60 It was reported320 that the incidence of bacteriuria is approximately 5% per day of catheterization, possibly explaining why UTIs are reported to account for between 25% and 50% of all NIs.42,320,321 The incidence-densities of UTIs vary from 3.3, to 7.6, to 10.1 episodes per 1,000 urinary catheter-days, respectively, in cardiothoracic, medical, and burn ICUs60 (Table 2). Most episodes are asymptomatic, and the associated low morbidity and mortality justifies that the surveillance for and treatment of asymptomatic nosocomial bacteriuria is not recommended for most ICU patients.321,322 However, this point needs to be reviewed in the case of immuno-suppressed patients.

The pathophysiology of UTI is characterized by a rapid colonization by microorganisms from the colonic flora along the urinary catheter. A quantitative culture of $\geq 10^5$ CFU/mL is the threshold admitted for a diagnosis of catheter-associated bacteriuria.323–326 Risk factors include the duration of catheterization, the absence of systemic antibiotic treatment, diabetes mellitus, and renal failure.320,326–328

Data from the 1980s79,329,330 has suggested that UTIs can prolong the length of a hospital stay by 1 to 3 days with a threefold probability of death during hospitalization. An attributable mortality rate of 12.7% was reported341 for urinary tract-related bacteremia in a study of bacteremia. However, this was not based on a strict case-control approach, and it should be viewed as an estimate and should be interpreted with caution. In a recent pooled analysis of 30 studies published between 1966 and 1998, Saint332 determined that bacteriuria would occur in 26% of hospitalized patients (95% CI, 23 to 29%) who have an indwelling catheter for 2 to 10 days. Among patients with bacteriuria, symptoms of UTI and bacteremia will develop in 24% of patients (95% CI, 16 to 32%) and 3.6% of patients (3.4 to 3.8%), respectively. The author further estimated that the additional costs of a case of UTI-related bacteremia would include the costs of microbiological analysis, antimicrobial therapy, and at least 2 extra days in the ward and 1 extra day in the ICU. However, the exact rate of UTI-related bacteremia remains a controversial issue, and Tambyah and Maki333 recently reported that secondary bacteremia developed in only 1 of 235 episodes (0.4%) of catheter-associated bacteriuria that complicated the course of 1,497 newly catheterized patients in a university hospital.

The prevention of catheter-related UTI has been a field of active clinical research since the demonstration 30 years ago that a closed drainage system significantly reduces the infection rate.322,327,334,335 As for any other device used in the management of critically ill patients, and is an apparently trivial concern compared to more sophisticated strategies, catheterization should be avoided when not strictly required and should be terminated as soon as possible.336,337 As compared with urethral catheters, suprapubic catheters have been demonstrated to be associated with a lower risk of UTI and a higher rate of satisfaction. They may also reduce the risk of local genitourinary complications such as prostatitis, epididymitis, or urethral stricture.338–344 The use of an external condom catheter has shown contradictory results.345–348 Although these alternative devices are not commonly used, further large randomized, controlled studies are needed in critically ill patients to define the place of these devices in the prevention of UTIs.337,349

Bladder irrigation with disinfectants and/or antibiotics, or their instillation in the drainage bag, is of limited benefit in the presence of closed systems, and the potential impact on the epidemiology of resistance currently argues against the recommendation of their use.337,350–352 Despite strong arguments in favor of the role of urethral meatus colonization in the pathophysiology, the results of two randomized controlled studies356,357 failed to demonstrate any benefit from rigorous cleansing, even when combined with topical antibiotic applications. Prophylaxis with systemic antibiotic therapy significantly reduces the incidence of catheter-associated UTIs but is of limited benefit for a catheterization time of < 3 days, and bacteriuria will develop in almost all patients after 2 weeks. In addition, the potential for adverse drug reactions and the selective pressure on the emergence of resistant strains have contributed to the lack of a routine recommendation for such prophylactic measures, with the exception of patients requiring specific urologic procedures.322,337,354,355

As for vascular access-related infections, the use of antiseptic-coated and/or antibiotic-coated catheters

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**Note:** The content provided is a natural language representation of the text, focusing on the core ideas and key points of the document. It has been condensed and summarized to highlight the main findings and discussions related to UTIs and their prevention in critical care settings. Further details and references can be found in the original document.
was demonstrated to be effective in the prevention of catheter-associated UTIs. A meta-analysis that included a total of 2,355 patients suggested that silver-oxide catheters, which are no longer available in the United States, were not associated with the significant reduction of UTIs (OR, 0.79; 95% CI, 0.57 to 1.10) that was, however, shown for silver alloy catheters (OR, 0.24; 95% CI, 0.11 to 0.52). However, major heterogeneity was observed between the eight randomized controlled studies retrieved from the 117 reports included in this analysis. A recent cost-effectiveness model suggested that, compared to standard catheters, this type of device may be associated with a modest cost saving of $4 in patients requiring catheterization for 2 to 10 days. Further studies are needed to assess whether these new devices should be used routinely or whether they should be considered for high-risk patients only.

**SSIs**

The prevention of SSIs relies on correct surgical technique, modification of host risk factors, and adequate antimicrobial prophylaxis. Trivial factors, which may be controlled by very simple measures, have been shown to significantly impact on SSI rates. Mild perioperative hypothermia is common in most patients undergoing surgery, and this may increase patients’ susceptibility to SSIs by causing vasoconstriction and impaired immunity. In an elegant prospective study, Kurz et al. demonstrated that the active maintenance of normothermia (mean ± SD temperature, 36.6 ± 0.5°C vs 34.7 ± 0.6°C; p < 0.001) reduced the SSI rate after colorectal surgery from 19 to 6% (6 of 104 patients compared to 18 of 96 patients, respectively; p = 0.009). An inverse relationship between subcutaneous tissue oxygen tension and SSI rates has been suggested. Greif et al. recently reported the impact of 80% supplemental oxygen during surgery and for 2 h after surgery in a cohort of 500 patients who had undergone elective colorectal resection. An SSI occurred in 13 of 250 patients (5.2%) who received this regimen compared with 28 of the 250 patients (11.2%) who received 30% supplemental oxygen only (absolute difference, 6.0%; 95% CI, 1.2 to 10.8%; p = 0.01).

The prophylactic administration of antibiotics can decrease postoperative morbidity, can shorten hospitalization, and can reduce the overall costs attributable to infections. However, prophylactic therapy should be used as little as possible with a spectrum of activity as narrow as possible to avoid the development of bacterial resistance. Antibiotic prophylaxis is clearly indicated for contaminated or clean-contaminated surgery and for clean operations such as those involved in the insertion of prosthetic devices, which are associated with a low risk of infection and high morbidity. Extension to other categories of clean procedures should be limited to patients with additional risk factors. Cefazolin (or cefoxitin when anaerobic coverage is necessary) remains the mainstay of prophylactic therapy. The selection of an alternate agent should be based on specific contraindications, local infection control surveillance data, and the results of clinical trials. To maximize its effectiveness, IV perioperative prophylaxis should be given within 30 to 60 min before the time of surgical incision (ie, at the induction of anesthesia in most cases).

Precise guidelines for specific surgical procedures have been published periodically, but many reports continue to describe inappropriate drug use such as invalid indications or the use of broad-spectrum drugs. Improving compliance with the guidelines must become one of the priority targets of infection control programs, which should ensure that they are adapted to local epidemiology or work conditions. One of the most beneficial measures in this setting is certainly the surveillance of SSIs. Periodic feedback to the surgical teams is the cornerstone of SSI prevention.

**Other NIs**

Hospital-acquired diarrhea may be of infectious or noninfectious origin. Common noninfectious causes include medication-induced changes in the colonic flora without acquisition of an enteric pathogen or changes secondary to enteral nutrition. Infection causes may be due to enteric pathogens of both endogenous and exogenous origin and often occur in outbreak situations. Bacteria, fungi, and viruses have been described as causes, but in a large majority of adults infections are due to *C. difficile*. First described in 1935, it was only identified as the etiologic agent of pseudomembranous enterocolitis at the end of the 1970s. This bacteria may be a resident of the human colon, where it does not cause disease until toxins are produced. The spectrum of disease includes asymptomatic carriage to mild watery diarrhea, severe diarrhea, and life-threatening pseudomembranous enterocolitis. *C. difficile*-related diarrhea is usually associated with the prior administration of antibiotics, of which clindamycin, combinations including β-lactamase inhibitors, and third-generation cephalosporins appear to confer the highest risk. Its acquisition is common in hospitalized patients, and cross-transmission has been related to transient carriage on the hands of HCWs and
contamination of the environment or to medical equipment such as electronic rectal thermometers. In addition, diarrhea may contribute to the spread of other resistant organisms such as VRE. In the presence of diarrhea, the diagnosis requires positive results for one of the following tests: pseudomembranes revealed by endoscopy; positive stool enzyme immunoassay for toxin A or B; or positive stool cultures. Diarrhea is treated with oral metronidazole, and colitis is treated with IV metronidazole. Oral vancomycin must be restricted to infrequent circumstances, considering its potential impact on the emergence of VRE. The testing of asymptomatic patients, including those who are asymptomatic after treatment, in an attempt to eradicate symptomless carriage is not recommended but may be debated in an outbreak situation.

Infection control measures are necessary to prevent the spread of this spore-forming organism, which is already capable of surviving in the hospital environment for prolonged periods. Measures have focused on improved hand hygiene compliance, barrier precautions, reduction of environmental contamination by cleansing and disinfection, and antibiotic restriction policies. Restricting clindamycin therapy was particularly successful in terminating outbreaks of *C. difficile* diarrhea associated with its use, but since almost all antimicrobial agents have been associated with *C. difficile* infection, overall restriction is recommended.

**Prevention of Infection in HCWs**

The protection of HCWs from the acquisition as well the transmission of infectious agents and the management of postexposure care are important tasks for hospital infection control programs. Precise guidelines have been published by the CDC Hospital Infection Control Practice Advisory Committee and are available at http://www.cdc.gov/ncidod/hip/guide/infectcont98.htm. The prevention strategies included in these recommendations include immunization for vaccine-preventable diseases, isolation precautions to prevent exposures to infectious agents, management of HCWs who have been exposed to infected patients, including postexposure prophylaxis, and work restrictions for exposed or infected HCWs.

Hospital policies should be edited for the medical personnel, including those not directly involved in patient care such as laboratory technicians, laundry workers, or transport teams. HCWs should be evaluated to assess their risk of acquiring or transmitting infection in the hospital to patients or other HCWs in a systematic pre-employment examination and eventual periodic examination. Immunization status must be checked and updated for tetanus, measles, rubella, mumps, pertussis, and hepatitis B. Some institutions also recommend serologic testing for varicella zoster virus and offer an attenuated vaccine for susceptible HCWs. Some authors have recommended hepatitis A vaccination for HCWs who are involved in pediatric care. Mantoux testing with appropriate follow-up should be systematic if the test results are positive. Outbreaks of influenza have been related to transmission by HCWs, and systematic yearly immunization should be encouraged. This not only reduces the influenza attack rates among patients, leading to substantial mortality rate among some subsets of patients, but may also reduce flu-like diseases and absences from work.

The prevention of transmission of any pathogen to HCWs, as to other patients and/or visitors, is based on the strict application of the guidelines for standard precautions and transmission-based precautions that already have been discussed (Table 9 and 10). All HCWs, not only doctors, nurses, and nursing assistants, but also respiratory and mobilization therapists, phlebotomists, radiology technicians, laboratory technicians, and transporters should receive initial training with refresher courses in the appropriate methods and techniques to avoid percutaneous, damaged skin, or mucus membrane contact with blood or other body fluid secretions.

Postexposure management of the HCWs is indicated for significant exposure to HIV, hepatitis B, *Neisseria meningitidis*, *Mycobacterium tuberculosis*, and varicella zoster virus. Detailed protocols should be immediately available 24 h per day through the emergency department or through a specialized infectious disease infection control consultant, and every exposure has to be the subject of an individualized evaluation to offer the best available management strategy.

**Conclusion**

The importance of nosocomial transmission in the ICU cannot be overemphasized. More than one third of NIs are acquired in ICUs, accounting for a crude incidence of 15 to 40% of hospital admissions, depending on the type of unit. Since more severely ill patients have higher risks for both acquiring NIs and for mortality, assessment of the mortality attributable to NIs in ICU patients is not straightforward. Nevertheless, NIs are definitely associated with substantial excess length of stay and additional hospital costs.

Although patients’ intrinsic risk factors for developing infections are difficult to modify, the risk of transmission of microorganisms can and should be
reduced to a minimum. An improved knowledge of the pathophysiology will help to understand the concepts of infection control. In this review, we have emphasized the transmission risks, which are particularly high in critically ill patients, and discussed the scientific background of precaution guidelines, which have been summarized in order to be appropriately implemented in the ICU.

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