The Role of the Intensive Care Unit Environment in the Pathogenesis and Prevention of Ventilator-Associated Pneumonia

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Summary

Ventilator-associated pneumonia is preceded by lower-respiratory-tract colonization by pathogenic microorganisms that derive from endogenous or exogenous sources. Most ventilator-associated pneumonias are the result of exogenous nosocomial colonization, especially, pneumonias caused by resistant bacteria, such as methicillin-resistant Staphylococcus aureus and multi-resistant Acinetobacter baumannii and Pseudomonas aeruginosa, or by Legionella species or filamentous fungi, such as Aspergillus. Exogenous colonization originates from a very wide variety of animate and inanimate sources in the intensive care unit environment. As a result, a strategic approach that combines measures to prevent cross-colonization with those that focus on oral hygiene and prevention of microaspiration of colonized oropharyngeal secretions should bring the greatest reduction in the risk of ventilator-associated pneumonia. This review examines strategies to prevent transmission of environmental pathogens to the vulnerable mechanically-ventilated patient. Key words: ventilator-associated pneumonia. [Respir Care 2005;50(6):813–836. © 2005 Daedalus Enterprises]
Introduction

Nearly 300,000 episodes of hospital-acquired pneumonia occur in United States hospitals each year.1 Most episodes of hospital-acquired pneumonia occur in patients undergoing mechanical ventilation, and ventilator-associated pneumonia (VAP) is the second most common nosocomial infection in United States intensive care units (ICUs) participating in the Centers for Disease Control and Prevention National Nosocomial Infection Surveillance program.2 VAP is associated with prolonged hospitalization (range, 6.5–25 d),3–6 increased health care costs (range, $8,800 to $41,000),4–8 and major attributable mortality (range, up to 30%).3,5,9–12 Prompt initiation of appropriate antimicrobial therapy reduces but does not eliminate adverse outcomes in patients with VAP.13–15 As a result, the primary goal of clinicians caring for mechanically ventilated patients should be to prevent VAP. In order to achieve this goal, an understanding of the epidemiology and pathogenesis of VAP is essential to design effective preventive strategies.

Epidemiology and Pathogenesis

Aerodigestive Colonization

VAP is most often the result of microaspiration of bacteria colonizing the aerodigestive tract (Fig. 1). The oropharynx appears to be the initial site of colonization in most cases of VAP; however, primary colonization of the stomach may precede oropharyngeal colonization in a proportion of cases.6 Following oropharyngeal colonization, contaminated oral secretions pool in the subglottic region above the endotracheal tube cuff. Subsequent microaspiration of contaminated subglottic secretions around the endotracheal tube cuff introduces pathogenic bacteria into the tracheobronchial tree and lower respiratory tract (see Fig. 1).

Aerodigestive colonization occurs endogenously or exogenously (see Fig. 1). With endogenous colonization, mechanically ventilated patients harbor potential pathogens in their oropharynx or gastrointestinal tract at the time of admission to the ICU, and these organisms may overgrow as a result of antimicrobial pressure and underlying illness.

With exogenous colonization, mechanically ventilated patients become colonized by nosocomial microorganisms after admission to the ICU, by one or more of the routes depicted in Figure 1. Nosocomial colonization is most often the result of horizontal cross-transmission from other colonized or infected patients in the ICU and is mediated through contact with the hands of transiently colonized health care workers.17–20 Alternatively, exogenous colonization may be the result of acquisition of pathogenic microorganisms from the inanimate ICU environment, on hospital surfaces, or in potable water that are transmitted to the susceptible patient through direct contact with the

Fig. 1. Routes of colonization/infection in mechanically ventilated patients. Colonization of the aerodigestive tract may occur endogenously (A and B) or exogenously (C through F). Exogenous colonization may result in primary colonization of the oropharynx or may be the result of direct inoculation into the lower respiratory tract during manipulations of respiratory equipment (D), during use of respiratory devices (E), or from contaminated aerosols (F).
source or, indirectly, through contacts with health care workers who have transiently acquired a nosocomial pathogen from an environmental source (see Fig. 1).

**Direct Inoculation of the Lower Airway**

Direct inoculation of the lower airway of a mechanically ventilated patient may also occur from endogenous and exogenous sources. Endogenous inoculation of the airway occurs as a result of microbial colonization of condensate in the inspiratory circuit of ventilatory tubing. Condensation within the circuit is most common in ventilators using bubble-through humidifiers, and colonization by microorganisms from the patient’s tracheobronchial mucosa is detectable within hours of tubing changes. Microorganisms within the inspiratory circuit can multiply to high concentrations and are deposited into the lower respiratory tract with position changes, suctioning, or other manipulation of the tubing. Exogenous colonization of the oropharynx and lower airway may occur from health care workers’ hands during manipulation of the airway or as a result of direct inoculation from a contaminated device or medical aerosol (see Fig. 1). Finally, direct inoculation of the airway may occur directly through aspiration of contaminated tap water or through airborne transmission of potential pathogens suspended in the ambient air of the ICU (eg, *Aspergillus* species or the severe acute respiratory syndrome [SARS] virus).

**Importance of Endogenous Versus Exogenous Colonization**

Recognizing that VAP can derive either from endogenous or exogenous colonization is essential to devise the most effective preventive strategies. If most episodes of VAP are of endogenous origin, then prevention needs to focus on enhancing oral hygiene to prevent oropharyngeal colonization and minimizing aspiration of colonization through supine positioning, continuous subglottic suctioning, or perhaps using endotracheal tubes with anti-infective surfaces (Table 1). However, if a substantial proportion of episodes of VAP are of exogenous origin—which appears to be the case, viewing the preponderance of cases caused by nosocomial organisms that are not part of the normal oropharyngeal flora, such as *Pseudomonas aeruginosa*, other multi-resistant Gram-negative bacilli, and *Staphylococcus aureus*, especially methicillin-resistant strains (MRSA)—then a combined approach that adds a variety of infection-control strategies designed to prevent exogenous colonization of the patient to efforts to improve oral hygiene and prevent aspiration of colonized secretions should provide optimal results (see Table 1).

Current consensus holds that most episodes of VAP derive from an endogenous source; however, Merrer et al found that 33% of patients colonized with MRSA in their ICU acquired their organism exogenously, and Bergmans et al found that 25% of VAP episodes caused by *P. aeruginosa* in a nonoutbreak setting were acquired by an exogenous route. Moreover, evidence from a large number of epidemics involving organisms that commonly cause VAP (Table 2) provides ample proof that cross-transmission from other patients or the inanimate environment is a huge problem that needs to be foremost when designing preventive interventions.

For example, Bukholm et al described an outbreak caused by *P. aeruginosa* during a 10-month period in which 14% of mechanically-ventilated patients developed infections by an identical clone, as determined by amplified fragment-length polymorphism. Despite revising hand hygiene and handling of respiratory equipment protocols, the outbreak continued unabated until a protocol that included weekly sterilization of water faucets and use of sterile water for administration of drugs and food was implemented. Likewise, Denton et al reported an outbreak in a neurosurgical ICU during a 13-month period where 27 isolates of *Acinetobacter baumannii* isolated from 19 patients were found to be clonal by pulsed-field gel electrophoresis and identical to isolates obtained from surfaces in the ICU and water. The number of isolates recovered from the environment correlated linearly with the number of patients colonized or infected with the outbreak strain, and control of the outbreak was ultimately achieved only after implementing aggressive environmental disinfection with hypochlorite. Finally, it is indisputable that the majority of nosocomial MRSA infections, including VAPs, derive from cross-transmission within the hospital, with undetected nosocomial colonization resulting in later nosocomial infection.

**Environmental Sources of Colonization**

**Animate Environment**

The hands of health care workers who have direct patient contact are invariably transiently colonized by nosocomial microorganisms that commonly cause VAP. Larson found that 21% of hospital employees’ hands were persistently colonized by Gram-negative bacilli, including *Acinetobacter*, *Klebsiella*, and *Enterobacter*. Goldmann et al found that as many as 75% of neonatal ICU health care workers’ hands were colonized by potentially pathogenic Gram-negative bacilli. Maki found that the hands of 64% of ICU personnel sampled at random were colonized at some time by *S. aureus*, and 100% showed transient carriage of a variety of Gram-negative bacilli at least once during the period of surveillance.
Without appropriate hand hygiene or wearing gloves, the hands of health care workers providing direct care to patients in the ICU become progressively colonized by pathogenic microorganisms. Moreover, health care workers’ hands readily become colonized by pathogenic microorganisms from handling contaminated equipment.
or touching inanimate surfaces contiguous to patients. Finally, breaks in hand hygiene have been directly implicated in numerous epidemics of VAP (see Table 2).

**Inanimate Environment**

The role of the inanimate environment in the transmission of nosocomial infections has been a subject of intense debate for decades. Prior to the 1970s, infection-control personnel routinely sampled hospital surfaces. It has been shown that bacterial contamination of hospital surfaces is common; floors and other surfaces in patient rooms, such as bed linens, bed rails, and tabletops, are almost universally contaminated by potentially pathogenic bacteria, such as *S. aureus*, enterococci, and Gram-negative bacilli such as *A. baumannii*. These studies, while demonstrating that the hospital environment is commonly contaminated, do not necessarily implicate the inanimate environment as a source of infection in hospitalized patients. However, studies are starting to show that the inanimate environment, while only rarely involved in the direct transmission of infection to patients, may well play an important indirect role in the nosocomial acquisition of pathogenic bacteria, contaminating health care workers’ hands and equipment (see Fig. 1).

**Hospital Surfaces.** As noted, a variety of nosocomial pathogens can be recovered from surfaces of the inanimate hospital environment. The capacity of these organisms to persist for weeks to months on surfaces such as tabletops, bed railings, and linens raises concern about indirect horizontal transmission of pathogenic microorganisms (see Fig. 1). Many Gram-positive organisms, especially enterococci and *S. aureus*, retain viability for periods in excess of 3 months when incorporated in dried organic materials commonly found on hospital surfaces.

In contrast, Gram-negative organisms subsist for much shorter periods, in the order of hours, with the exception of *Klebsiella* species, *Acinetobacter* species, and *Enterobacter* species, which can retain viability for several days. The capacity of surface organisms to secondarily contaminate health care worker’s hands and clothes without any direct patient contact provides support for the role of hospital surfaces in the horizontal spread of hospital pathogens.

**Health Care Worker Clothing and Equipment.** A number of recent studies have found heavy bacterial contamination of personal-use and patient-care items, including clothing, stethoscopes, electrocardiographic leads, blood pressure cuffs, pagers, and computers. Marinella et al found that 38% of health care worker’s stethoscopes, sampled randomly, were contaminated by *S. aureus*, and these researchers documented transmission from a stethoscope to a volunteer’s skin.

### Table 2. Published Outbreaks of Hospital-Associated Bacterial Pneumonia Caused by Selected Bacterial Pathogens

<table>
<thead>
<tr>
<th>Bacteria Species</th>
<th>Total Number of Studies</th>
<th>Hospital Surfaces</th>
<th>Health Care Workers’ Hands</th>
<th>Tap Water</th>
<th>Respiratory Therapy Equipment</th>
<th>Bronchoscope</th>
<th>Multi-dose Medical Aerosols</th>
<th>Other/Not Specified</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acinetobacter</td>
<td>23</td>
<td>18, 20, 46–54</td>
<td>20, 55–57</td>
<td>NA</td>
<td>20, 22, 48, 58–62</td>
<td>NA</td>
<td>NA</td>
<td>17, 57, 63–65</td>
</tr>
<tr>
<td>Burkholderia cepacia</td>
<td>10</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>66–70</td>
<td>NA</td>
<td>71–73</td>
<td>74, 75</td>
</tr>
<tr>
<td>Enterobacter</td>
<td>4</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>76–79</td>
<td></td>
</tr>
<tr>
<td>Klebsiella</td>
<td>9</td>
<td>80</td>
<td>81–83</td>
<td>81, 82</td>
<td>130</td>
<td>NA</td>
<td>84</td>
<td>85–89</td>
</tr>
<tr>
<td>Legionella</td>
<td>61</td>
<td>NA</td>
<td>90–125</td>
<td>102, 126–129</td>
<td>(transesophageal echocardiogram probe)</td>
<td>NA</td>
<td>131–147</td>
<td></td>
</tr>
<tr>
<td>Staphylococcus</td>
<td>6</td>
<td>177</td>
<td>177–179</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>175, 180, 181</td>
</tr>
</tbody>
</table>

*The references were identified by a MEDLINE search, using the medical subject headings, “disease outbreak,” “cross infection” or “epidemic,” cross-referenced with the specific bacteria group. NA = not applicable.*
scopes and blood pressure cuffs for all ICU patients (see Table 1).

In contrast, innumerable outbreaks of VAP have been traced to contamination of respiratory therapy equipment and diagnostic equipment such as bronchoscopes and endoscopes. Takigawa et al reported 16 episodes of hospital-acquired pneumonia caused by *Burkholderia cepacia*, which stemmed from contamination of inhaled-medication nebulizer reservoirs. Likewise, Srinivasan et al reported 28 episodes of pneumonia caused by *P. aeruginosa* linked epidemiologically to contaminated bronchoscopes with defective biopsy-port caps; this outbreak occurred despite adherence to disinfection and sterilization guidelines. The importance of strict adherence to recommended policies and procedures for cleaning and reprocessing of respiratory therapy and diagnostic equipment cannot be overemphasized (see Table 1).

**Hospital Water.** A variety of microorganisms, including many Gram-negative bacilli, mycobacteria, fungi, and parasites, can be isolated from hospital water and have been implicated in endemic and epidemic nosocomial infections (see Table 2). Many of these outbreaks were caused by bacteria typically thought of as “water” organisms, such as *P. aeruginosa*, *Stenotrophomonas maltophilia*, and *A. baumannii*; however, the most important and epidemiologically linked water pathogen is the *Legionella* group.

The first reports describing *Legionella* species as a human pathogen were published in 1976. The genus is composed of 48 different species and 70 different serotypes, although *Legionella pneumophila* accounts for the vast majority of human infections (>90%), and other species such as *Legionella longbeachae*, *Legionella bozemanii*, and *Legionella micdadei* are encountered less commonly. Nosocomial legionellosis was first described in 1979, and it is estimated that 25–45% of all cases of legionellosis are acquired in the health care setting, with a mortality that approaches 30%. Contamination of hospital potable water remains underappreciated, despite studies showing *Legionella* species can be recovered from 12–70% of hospital water systems, and studies in which nosocomial cases were identified only when recommended diagnostic and surveillance methods were employed.

Characteristics of hospital water systems associated with *Legionella* contamination include piping with dead-ends that facilitate stagnation, large-volume water heaters that result in inefficient heating of hospital water, sediment build-up, water-heater temperatures <60°C, tap water temperatures <50°C, water pH <8, and receiving municipal water untreated with monochloramine. Hospital Air. Filamentous fungi and molds, such as *Aspergillus* species, *Fusarium* species, and *Mucorales*, are found near-universally in ambient air, and more than 2 decades ago infections caused by these organisms were considered a curiosity. The huge numbers of immunocompromised patients in the population as a result of organ transplantation, intensive cancer chemotherapy, and acquired immune deficiency syndrome have changed this view dramatically. Nosocomial infections with filamentous fungi are clearly aerogenically-acquired in the vast majority of cases, and numerous outbreaks have been linked to hospital construction or breakdowns in hospital air-handling systems. Pegues et al reported a remarkable outbreak of invasive pulmonary aspergillosis among orthotopic liver-transplant recipients, traced to massive aerosolization of spores following wound-dressing changes in a patient with a surgical wound infection caused by *Aspergillus fumigatus*. Ultra-filtration of ambient air using high-efficiency-particulate-arrestor (HEPA) filtration systems for patients at risk greatly reduces the risk of nosocomial filamentous fungal infections in vulnerable hospitalized patients (see Table 1).

The Need for a More Comprehensive Approach to the Prevention of VAP That Acknowledges the Important Role of the Hospital Environment

Most published evidence-based guidelines for the prevention of VAP have focused on measures to improve oral hygiene, prevent aspiration of microbe-laden oropharyngeal secretions, novel approaches to suppress the aerodigestive flora, and assuring the safety of respiratory therapy equipment and medical aerosols (see Table 1). The role of the ICU environment in nosocomial infection must be acknowledged when devising strategies to prevent nosocomial colonization of the highly susceptible ventilated patient by MRSA and multi-resistant Gram-negative bacilli and secondary VAP (see Table 1). Unfortunately, other than acknowledging potable water as a potential source of nosocomial legionellosis and ambient air as the natural reservoir of nosocomial filamentous fungi, we believe that the role of the ICU environment in nosocomial infections, especially VAP, remains vastly underappreciated. We now examine infection-control strategies designed to reduce cross-transmission of nosocomial pathogens.

**Organizational Structure**

The capacity to systematically improve the care of mechanically ventilated patients and prevent VAP requires a structural foundation upon which the processes of care can be optimized (ie, striving to make it easy for health care workers to do it right and difficult to do it wrong) (see
Table 1). Accountability for compliance with critical policies and procedures and assessment of outcomes needs to be built into the administrative structure of the ICU.

ICUs should be designed with the user in mind, ensuring appropriate space, resources, and environment for day-to-day operations. For example, Mulin et al found that converting from an open unit to single ICU rooms greatly reduced colonization by A. baumannii. Materials used for fixtures, furniture, and other surfaces should be smooth and easy to clean, as surfaces made of porous materials are more likely to support bacterial colonization. Finally, placing hand-hygiene stations—in convenient locations in the clinical areas of the hospital improves compliance with hand hygiene. Many of the published recommendations for ICU architectural design are empirical, and evidence that they reduce rates of nosocomial infection is, by and large, lacking. Much more research is needed before specific features of ICU design achieve the level of an evidence-based guideline.

Perhaps more important than the architecture of the ICU is its staffing: an ICU must be adequately staffed to allow the processes of care to be carried out but also assure a high level of compliance with essential infection-control practices such as hand hygiene and barrier isolation (see Table 1). Adequate staffing cannot be overemphasized: numerous studies have found greatly increased rates of nosocomial infection when ICUs are staffed suboptimally or when staffing requirements are met by temporary personnel who are unfamiliar with institutional policies and procedures. In a large nosocomial outbreak of Enterobacter cloacae infection in a neonatal ICU, Harbarth et al found that infection rates during periods of understaffing were strikingly higher than during periods with adequate staffing levels (risk ratio 6.0, 95% confidence interval 2.2–16.4). The consequences of understaffing have included targeted education, feedback, convenient location of sinks and hand hygiene agents, use of alternative, less irritating hand-hygiene agents, and education of patients.

Hygienic hand care with antiseptics is clearly more effective than conventional hand-washing with soap and water; the advantage is most pronounced when contamination is heavy. Conventional hand-washing with plain soap and water results in minimal reduction or, paradoxically, an increase in bacterial yield compared to baseline counts of sampled hands. The increase is probably caused by promotion of bacterial release and dispersal through shedding of colonized skin squames. In addition to superior antimicrobial activity, some antiseptics such as chlorhexidine bind to the stratum corneum, producing long-term anti-infective activity on the skin surface.

Studies of hand hygiene that used rates of nosocomial colonization or infection as the primary outcome measure are summarized in Table 3. Most of these studies were limited by lack of randomization or concurrent implementation of other infection-control interventions, making the impact of the hand hygiene program difficult to assess precisely. Moreover, the Hawthorne effect clouds application of the short-term results of an intervention to the long term. Nonetheless, 3 prospective randomized controlled trials of chlorhexidine compared with nongermicidal soap or isopropyl alcohol found that conventional hand-washing with 2–4% chlorhexidine was associated with a 27–47% relative risk reduction in nosocomial infection in the ICU.

Alcohol-based, waterless hand rubs or gels are now advocated by the Centers for Disease Control and Prevention for hand hygiene because of their convenience and broad-spectrum activity, but also because they appear to preserve hand condition better than antiseptic soap and water. A vigorous one-minute rubbing with a sufficient volume of alcohol to wet the hands completely has been shown to be highly effective at reducing the density of skin flora. Ethanol, iso- and n-propanol are the constituents of most commercially available alcohol-based hand rubs; at equal concentrations, n-propanol is most effective, and ethanol the least. However, all have limited efficacy with gross...
soilage, so that visibly soiled hands must always be washed with antiseptic soap and water. Moreover, at least 3 mL of an alcohol-based rub is needed to completely coat the hands and achieve optimal degerming. Finally, alcohol-based rubs do not possess anti-sporicidal activity, and a standard soap-and-water hand wash should be employed, prior to use of alcohol-based rubs, before and after contact with patients infected by *Clostridium difficile*.253

Alcohol-based hand gels have recently been introduced in an attempt to reduce the drying effects of alcohol-based handrubs and have come into wide use throughout the United States. Their composition is similar to that of hand rubs, but gels also contain thickening agents to enhance their viscosity. Two recent studies have reported reduced antibacterial efficacy of alcohol gels compared to a reference alcohol handrub solution (2-propanol 60% volume/volume),288,289 and a recent interventional cohort study of a 60% alcohol-based hand gel in 3 pediatric ICUs found only a modest improvement in compliance with the gel, compared with conventional hand-washing with soap and water (8% increase, p < 0.001); moreover, only 45% of staff members reported satisfaction with use of the hand gel.289a

A recent review describes in detail the various hand hygiene agents available and their spectrum of activity.266

### Table 3. Prospective Studies of Available Hand Hygiene Products With Nosocomial Infection Rates As the Outcome Measure

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Patients</th>
<th>Study Design</th>
<th>Comparator</th>
<th>Risk Reduction (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol Handrub</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fendler et al271</td>
<td>NR</td>
<td>Nonrandomized comparative trial</td>
<td>0.3% chloroxylenol</td>
<td>0.70 (0.59–0.83)*</td>
</tr>
<tr>
<td>Hilburn et al272</td>
<td>NR</td>
<td>Before-after trial</td>
<td>0.3% chloroxylenol</td>
<td>0.64 (0.41–1.00)†</td>
</tr>
<tr>
<td>Mody et al273</td>
<td>NR</td>
<td>Before-after trial</td>
<td>Nongermicidal soap</td>
<td>1.02 (NR)†</td>
</tr>
<tr>
<td>Brown et al274</td>
<td>248</td>
<td>Before-after trial</td>
<td>Nongermicidal soap</td>
<td>0.14 (NR)†</td>
</tr>
<tr>
<td>Lai et al275</td>
<td>NR</td>
<td>Before-after trial</td>
<td>NR</td>
<td>0.25 (NR)*</td>
</tr>
<tr>
<td>Parienti et al276</td>
<td>4,387</td>
<td>Prospective randomized equivalence trial</td>
<td>4% Povidone-iodine and 4% chlorhexidine</td>
<td>1.03 (0.67–1.42)†</td>
</tr>
<tr>
<td>Gundlapalli et al277</td>
<td>NR</td>
<td>Before-after trial</td>
<td>NR</td>
<td>NR-VRE infecton rates unchanged†</td>
</tr>
<tr>
<td>Pittet et al282</td>
<td>NR</td>
<td>Before-after trial</td>
<td>NR</td>
<td>0.43 (NR)*</td>
</tr>
<tr>
<td>All studies</td>
<td></td>
<td></td>
<td></td>
<td>0.14–1.03</td>
</tr>
<tr>
<td>Triclosan</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zafar et al278</td>
<td>22</td>
<td>Before-after trial</td>
<td>Chlorhexidine</td>
<td>NR-outbreak terminated</td>
</tr>
<tr>
<td>Webster et al279</td>
<td>1,916</td>
<td>Before-after trial</td>
<td>Chlorhexidine</td>
<td>0.55 (0.33–0.92)*</td>
</tr>
<tr>
<td>Chlorhexidine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Massanari et al280</td>
<td>5,389</td>
<td>Crossover trial</td>
<td>Nongermicidal soap</td>
<td>0.53 (NR)*</td>
</tr>
<tr>
<td>Doebbeling et al281</td>
<td>1,894</td>
<td>Crossover trial</td>
<td>Isopropyl alcohol</td>
<td>0.73 (0.59–0.90)*</td>
</tr>
<tr>
<td>Maki et al282</td>
<td>NR</td>
<td>Crossover trial</td>
<td>Nongermicidal soap</td>
<td>0.60 (NR)*</td>
</tr>
<tr>
<td>Casewell et al283</td>
<td>NR</td>
<td>Crossover trial</td>
<td>NR</td>
<td>0.6 (NR)*</td>
</tr>
<tr>
<td>All studies</td>
<td></td>
<td></td>
<td></td>
<td>0.53–0.73</td>
</tr>
<tr>
<td>Parachlorometaxylenol</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simmons et al283</td>
<td>589</td>
<td>Before-after trial</td>
<td>NR</td>
<td>1.03 (NR)†</td>
</tr>
<tr>
<td>Povidone-Iodine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maki et al282</td>
<td>NR</td>
<td>Crossover trial</td>
<td>Nongermicidal soap</td>
<td>0.61 (NR)*</td>
</tr>
<tr>
<td>Massanari et al280</td>
<td>NR</td>
<td>Crossover trial</td>
<td>Nongermicidal soap</td>
<td>0.54 (NR)*</td>
</tr>
</tbody>
</table>

* p < 0.05
† p > 0.05
NR = not reported
VRE = vancomycin-resistant enterococcus
Microbial Surveillance and Targeted Isolation. Isolation of infected and colonized patients is widely regarded as the most effective way to prevent spread of resistant pathogens through the health care institution. Unfortunately, the present practice of identifying and isolating patients who develop an infection with antimicrobial-resistant organisms fails to identify the far larger population of patients asymptotically colonized. For every patient known to be colonized or infected by MRSA, vancomycin-resistant enterococci, multi-resistant Gram-negative bacilli or C. difficile—because of serendipitous clinical cultures—there are 3–5 patients on average on that same unit with undetected colonization by the resistant species (Fig. 2).

The implication of this “iceberg phenomenon” is that most cross-transmission of resistant microorganisms occurs between patients without signs or symptoms of infection. That colonization is a prerequisite for infection with multi-resistant organisms in the hospital environment has been shown in numerous studies. Pujo et al showed that the most important risk factor for MRSA bacteremia in an ICU population was MRSA nasal carriage (risk ratio 3.9, 95% confidence interval 1.6–9.8), with a far higher risk of invasive nosocomial infection associated with colonization by MRSA than by methicillin-susceptible strains of S. aureus (38% vs 9.5%). Muder et al found a similarly increased risk of nosocomial infection with MRSA carriage (risk ratio 3.8, 95% confidence interval 2.0–6.4). A recent prospective study found that 14 (1.1%) of 1,278 patients found to be nasal S. aureus carriers on admission to the hospital subsequently developed concordant nosocomial S. aureus bacteremia. Institutional infection-control programs must find strategies to more effectively prevent nosocomial colonization of susceptible patients by all multi-resistant organisms to successfully control the rising tide of resistance.

A recent guideline from the Society for Healthcare Epidemiology of America recommends proactive microbiologic screening policies to detect the presence of silent colonization in high-risk patients (see Table 1). The majority of patients admitted to ICUs would be considered high-risk under these new recommendations, which mandate screening a very large proportion of the patients, or better, all of them. Weekly surveillance cultures, as performed in the majority of studies that have used this approach, require major laboratory support and are very labor-intensive. Moreover, by the time the results of surveillance cultures showing colonization by a resistant organism become available and isolation precautions can be implemented, precious time has passed, providing opportunities for further spread of the organism. Finally, targeted screening for only one nosocomial pathogen, such as vancomycin-resistant enterococci, ignores the possibility that the patient might be colonized by nosocomial pathogens other than vancomycin-resistant enterococci, which obviously facilitates their spread.

Despite notable successes, most of the studies examining the effectiveness of an active microbiologic surveillance with isolation suffer from a number of methodological flaws that limit their generalizability, and this approach has recently failed to control the transmission of MRSA in one well designed study.

Preemptive Barrier Precautions. A simpler and perhaps more logical strategy for preventing spread of all types of pathogenic bacteria is the preemptive use of barrier precautions in all high-risk patients (see Table 1). Under this approach, patients are placed in isolation from the time of ICU admission, in order to prevent health care workers from acquiring hand contamination by pathogenic organisms when having contact with patients with unrecognized colonization or the contaminated inanimate environment, and to block transmission to other as-yet-uncolonized patients. Numerous studies have shown that the preemptive use of barrier precautions, also called “protective isolation,” can effectively prevent the spread of multi-resistant organisms such as MRSA or vancomycin-resistant enterococci in an epidemic setting, and other studies have shown the effectiveness of protective isola-
tion in high-risk populations, such as patients in an ICU, for prevention of endemic nosocomial infection, including by multi-resistant organisms.\textsuperscript{296,344–354}

Preemptive barrier precautions can involve a number of levels, including simply wearing gloves for all patient contacts, wearing gowns in addition to gloves for all patient contacts, and using dedicated equipment in all rooms in addition to gowns and gloves.

**Routine Gloving.** The routine use of gloves when handling or touching invasive devices, nonintact skin, or secretions are already considered a part of standard precautions;\textsuperscript{355} however, donning gloves for every contact with the patient or their environment represents an added level of hygiene that may reduce the risk of cross-transmission of pathogenic bacteria. Johnson et al demonstrated a 4-fold reduction in rates of *C. difficile* infections on hospital wards where health care workers donned gloves prior to every patient contact, regardless of the presence or absence of gastrointestinal symptoms.\textsuperscript{347} Likewise, Leclair et al found that routinely wearing gloves prior to contact with pediatric patients reduced nosocomial rates of respiratory syncytial virus infection 3-fold.\textsuperscript{345}

A routine gloving policy is conceptually attractive from an infection-control standpoint; however, more studies demonstrating its benefit are needed before general recommendations can be made. Moreover, untoward side effects from a routine gloving policy may occur if their proper use is not ensured, as gloves become colonized with pathogenic bacteria just as easily as ungloved hands. This was highlighted during an ICU outbreak due to *Acinetobacter calcoaceticus* variety *anitratus*, where a failure by health care workers to replace gloves between patient encounters increased cross-transmission between patients.\textsuperscript{56} In addition, wearing gloves does not ensure that the health care workers’ hands will remain free of pathogenic bacteria, as Tenorio et al found that nearly 30% of health care workers’ hands became colonized with vancomycin-resistant enterococci (vancomycin-resistant enterococci) after patient contact, despite the appropriate use of gloves.\textsuperscript{356} These examples highlight the importance of hand hygiene that includes disinfecting hands prior to donning and after removing gloves.\textsuperscript{253}

**Protective Gowning.** The role that gowns play in interruption of transmission remains unclear. Some studies have shown successful control of outbreaks only when gowns were used in addition to gloves.\textsuperscript{295,353,357–359} Two recent quasi-experimental studies reported decreased nosocomial transmission of vancomycin-resistant enterococci with the use of gowns in addition to gloves.\textsuperscript{353,360} However, Slaughter et al, in a nonrandomized controlled trial, did not find that gowns provided an incremental advantage for preventing rectal colonization with vancomycin-resistant enterococci.\textsuperscript{349} Requirement of a greater level of precautions may implicitly improve compliance.\textsuperscript{265,361} Lai et al reported 100% compliance with hand-washing after contact with patients in strict isolation; in contrast, there was only 50% compliance after contact with patients not in isolation.\textsuperscript{362}

Gowns, however, add to the cost of barrier precautions.\textsuperscript{363} Studies are needed to better clarify the necessity for gowns, in addition to gloves, in preventing the spread of resistant bacteria, and to determine whether improved compliance with hand-washing and preemptive glove use can obviate gowns for the prevention of nosocomial spread. We believe that gowns should be used in situations where there is high potential for self-contamination (large open wounds, fecal incontinence).

**Dedicated Equipment.** The use of dedicated equipment in isolation rooms of patients known to be colonized with multi-resistant bacteria is a standard component of contact isolation\textsuperscript{355} (see Table 1), despite an absence of studies demonstrating its benefit. That said, the demonstration of ready cross-transmission of pathogenic bacteria through common use items such as rectal thermometers,\textsuperscript{364} electrocardiogram leads,\textsuperscript{202} and blood pressure cuffs\textsuperscript{303} suggests that this measure is theoretically sound. Whether the routine use of dedicated equipment with all ICU patients can reduce rates of nosocomial infection requires further study.

The available studies show that the use of preemptive barriers can reduce the spread of multi-resistant bacteria; however, their impact on rates of VAP is less clear. Moreover, it is unknown whether a preemptive barrier policy would be cost effective. However, it is clear that the current methods to control the spread of multi-resistant bacteria have failed dismally, and it is time to examine alternative paradigms.

**Prevention of Infections Caused by Respiratory Devices**

Following bronchoscopy, endoscopes are typically contaminated with $6 \times 10^2 \text{ colony-forming units (CFU)/mL}$,\textsuperscript{365} and as noted, a number of outbreaks have been traced to defective or improperly reprocessed bronchoscopes.\textsuperscript{24–27,211–213} Flexible endoscopes used for bronchoscopy are considered semicritical medical devices by the Spaulding classification and therefore require high-level disinfection following use.\textsuperscript{366} In order to ensure their safe use, all flexible endoscopes should be reprocessed with the following procedures: (1) physical cleaning to reduce microbial bioburden and remove organic debris, (2) high-level disinfection—glutaraldehyde and automated chemical sterilizing systems that use peracetic acid are most commonly used in the United States.
States—with adequate contact time between the disinfectant and device surface, (3) following disinfection, rinsing the device with sterile or filtered tap water to remove disinfectant residue, (4) flushing of all channels with 70–90% ethyl or isopropyl alcohol, and (5) drying with forced air. Devices used with endoscopes that violate mucosal barriers, such as biopsy forceps, should be reprocessed as critical medical items with full sterilization. Other devices used in the delivery of respiratory care are highlighted in Table 4. Like endoscopes used for bronchoscopy, these devices are considered semicritical under the Spaulding classification and therefore should be reprocessed in a manner similar to endoscopes prior to reuse.

The management of ventilator circuits, humidification, and suction catheters deserves special attention. Condensate forms in the inspiratory circuit of ventilator tubing in patients ventilated with systems using bubble-through humidifiers because of differences in temperature between inspired gases and ambient air. Condensate can become contaminated by bacteria from the patient’s endogenous flora, which multiply to high levels, and if heavily contaminated condensate is inadvertently bolused back into the patient’s airway, infection can ensue. Periodic drainage of condensate in the inspiratory circuit is recommended (see Table 1); however, the practice of changing ventilatory circuits every 48 hours has not been shown to be superior to changing ventilator tubing every 7 days, and may actually increase the risk of VAP, compared to longer-interval circuit changes.

The use of heat-and-moisture exchangers rather than bubble-through humidifiers can significantly reduce rates of inspiratory circuit condensate contamination and in one controlled trial, the rate of VAP was reduced from 16% to 6% (p < 0.05) in patients randomized to the heat-and-moisture exchanger (see Table 1).

Suctioning of airways to clear secretions is a routine part of airway management in patients receiving mechanical ventilation. Suctioning may be performed using either a single-use disposable suction catheter or a closed, reusable in-line suction system. Closed systems are attractive because they simplify care of patients and can reduce costs; however, they may be associated with increased colonization of airways. However, studies have not found an increased rate of VAP in patients ventilated with closed-suction systems, although at least one study has found that the use of a closed-suction system was associated with a trend toward a reduction in the rate of VAP (from 15.9 to 7.3 per 1,000 ventilator days, p = 0.07).

Prevention of Infections Caused by *Legionella* Species

Despite the ubiquity of water systems colonized with *Legionella* species and studies demonstrating a correlation between the level of colonization and risk of infection, the Centers for Disease Control and Prevention does not recommend routine culture surveillance of hospital water systems, although this stance is controversial. Researchers from Pittsburgh and the Allegheny County Health Department have recommended a stepped approach that involves initial surveillance of hospital water for *Legionella* contamination, regardless of the presence or absence of institutional nosocomial legionellosis, followed by continued surveillance based on the level of contamination found or the occurrence of institutional legionellosis.

*Legionella* species are resistant to chlorine and heat, making them challenging to eradicate from hospital water systems. Attempts to hyperchlorinate hospital water have been partially successful if chlorine levels are maintained between 2 and 6 parts per million at all times, but this produces accelerated corrosion, and continuous chlorination is expensive. Thermal eradication is also feasible, using a “heat-and-flush” method to raise water tank temperatures to > 70°C and distal water sites to > 60°C for short periods. While effective, this method is labor-intensive, and there is always the fear that patients may sustain scald injuries if they are not instructed to avoid using tap water during the flush period. The use of technologies such as instantaneous steam heat for incoming water and ultraviolet light are technically feasible.
with newer hospital water systems, but may be incompatible with older systems.

Perhaps the most attractive, effective, safe and cost-efficient method for Legionella eradication may be the use of continuous copper-silver ionization systems to sterilize hospital water (see Table 1). These systems have been well studied over the past decade and have proven to be highly effective for eradicating Legionella contamination of hospital water and, most importantly, preventing nosocomial legionellosis in institutions when other interventions had failed.380 In our own institution, 2 clusters of nosocomial legionellosis prompted a retrospective review that identified 15 cases over a 17-year period. Surveillance of the hospital water system found that 35% of all samples contained low levels of L. pneumophila, which were shown to be clonally related to isolates from cases of nosocomial legionellosis. Installation of a continuous copper-silver ionization system in 1993 led to complete eradication of Legionella from water samples, and no further cases of nosocomial legionellosis have been identified at our institution since that time.

**Prevention of Infections Caused by Filamentous Fungi**

Studies performed nearly 20 years ago demonstrated that interventions designed to reduce counts of mold spores in hospital air could greatly reduce the risk of devastating invasive aspergillus infections in-patients at high risk of opportunistic infections (see Table 1). Sherertz et al found that installation of HEPA filters on a bone-marrow-transplant ward reduced aspergillus spore counts from 1–15 to 0.009 spores/m³.243 14 cases of invasive aspergillosis were identified among hematology patients housed on units without HEPA air filtration, as contrasted with no cases in patients cared for on HEPA-filtered wards. In another study, 50% of patients undergoing bone-marrow transplantation developed invasive aspergillosis while housed on a non-filtered ward, and rates of invasive aspergillosis remained unchanged, even with the use of prophylactic amphotericin B deoxycholate (incidence of invasive aspergillosis 43%); when patients were cared for on a HEPA-filtered unit, the incidence of invasive aspergillosis dropped to 0% during the study period.244

Despite the routine availability of HEPA filtration on hospital units caring for immunocompromised patients at high risk, opportunistic filamentous fungal infections still occur. Many of these infections occur as a result of nosocomial acquisition outside of the hospital after they have been discharged.381 Studies have demonstrated a reduction in very early invasive fungal infections (< 40 d after transplant) and a rise in very late invasive fungal infections (> 6 mo after transplant),382 and molecular epidemiologic studies have shown a lack of concordance between hospital environmental and clinical isolates.383,384 Yet nosocomial invasive fungal infections still occur, most often in occurrence with breaks in HEPA filtration, improper masking of compromised patients when off of their protected unit, and especially during periods of hospital construction.227–237 In order to prevent these devastating infections, hospitals must ensure that their HEPA filters are maintained and monitored at regular intervals and that vulnerable patients wear high-efficiency masks when they leave their protected unit for tests or procedures (see Table 1).385

The impact of ongoing institutional renovation and construction on the risk of invasive aspergillosis cannot be overstated. Hospitals must make every effort to ensure the safety of their compromised patient populations during the planning and implementation stages of all construction projects (see Table 1). Close collaboration between engineers and infection-control professionals is mandatory to judge the probable level of environmental contamination with every planned project, and pre-planned control measures must be in place and tested before any project is commenced. The use of laminar airflow ventilation during periods of construction,386 the taping of all windows, and the restriction of transplants during periods of construction have each been shown to be beneficial in studies.387,388

At our institution we have successfully employed a process in which all hospital renovation sites are completely sealed and made negative to adjacent areas by venting air directly to the outside or through a HEPA filter back into...
the hospital air system. As an additional level of precaution, portable HEPA filters are placed within renovation sites during projects of high risk. Air sampling studies have shown that spore loads are often 50–100 times higher than baseline within renovation sites (eg, >300 colony-forming units/L), but spore loads in areas immediately adjacent to these sites can be maintained at very low levels (eg, 1–4 colony-forming units/L) with implementation of the institutional protocol (Fig. 3).

Summary

Though current consensus suggests that most episodes of VAP derive from an endogenous source, a considerable amount of data suggests that a major portion of these infections are acquired exogenously from the hospital and ICU environment, especially infections caused by multiresistant bacteria—MRSA, Acinetobacter species, and Pseudomonas species—Legionella, and filamentous fungi. Preventive programs that combine infection-control strategies to prevent cross-colonization by nosocomial microorganisms and detailed protocols to assure environmental safety with measures that focus on improving oropharyngeal hygiene and preventing aspiration of colonized secretions are likely to be most effective. Future research on prevention of VAP must focus on ways to improve compliance with hand hygiene over the long term and determine whether the routine use of preemptive barrier isolation in ICUs can significantly reduce rates of VAP.

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The Role of the ICU Environment in Ventilator-Associated Pneumonia


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Sammartino MT, Israel RH, Magnusen CR. Pseudomonas aerugi-


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Aspergillus terreus.
patients: associations with building hygiene, design, and indoor air.


THE ROLE OF THE ICU ENVIRONMENT IN VENTILATOR-ASSOCIATED PNEUMONIA


Discussion

Kollef: We finished some survey studies that Vicky Frazer’s group in our hospital did, looking at patients in our surgical units, and we’re doing them in the medical ICUs as well. It turns out that about 15% of the patients will have MRSA as soon as they come into the ICU, and that’s just one organism. These are presumably “clean” patients who are getting elective operations or come in with trauma, and they end up in the surgical unit with MRSA. So when you say preemptive isolation and barrier precautions, some people have taken the opposite argument and have said, well if it’s out there already, why bother? I know of hospitals that have done that.

REFERENCE


Maki: Some of the most esteemed centers in the world have abandoned isolation precautions for MRSA. I think this is a “head in the sand” position. But as to the statement that 15% of patients are positive for MRSA on admission to the unit, there are a growing number of studies now that show that in a general population in the United States, 3–5% of healthy people carry MRSA. That’s what they’re finding in new recruits at Brooke Army Medical Center and in civilian studies. This is an even more powerful argument that we ought to be using preemptive isolation. Why should we increase the likelihood that MRSA will spread to other vulnerable patients?
Kollef: I agree with you. I’m just saying that I think the other part of this (which Dave Pierson alluded to earlier) is the dollars. I think sometimes hospitals and chief executive officers look at the initial fixed costs of something such as putting patients on preemptive isolation, and don’t focus so much on what the other costs may be.

Maki: If we can cut MRSA infections 40 percent—most of the studies suggest we can if we do it, and MRSA infection is very expensive—you don’t have to prevent very many MRSA infections to pay for all the cost of the additional barrier precautions you use in a year. What I find most striking is that we bought “universal precautions” hook, line, and sinker 15–18 years ago with no data. Do you know what the number-needed-to-treat is to prevent a case of HIV [human immunodeficiency virus] in exposed health care workers? It’s astronomical. I’ve tried to cost it out; it’s probably somewhere in the range of half a billion dollars to prevent one case of HIV by universal precautions, focusing on barriers. And I’m not even talking about sharps injury precaution, which is far more important: just barriers. But we don’t use barriers properly. There is a role for universal precautions; unfortunately, they are not used properly to protect patients from resistant infections. If we simply used universal-precautions barriers properly, we would have much more benefit, and we’d save money.

Solomkin: I want to follow up on a comment you made about that study on colistin aerosolization, which was in an era before carbapenems and broad-spectrum penicillins. Was colistin resistance seen?

REFERENCES

Solomkin: We are using it on a small number of patients who were colonized with a multi-drug resistant pseudomonas. We use it prophylactically.

Maki: We’re not doing it prophylactically as a therapeutic adjunct yet, but we do it if we have evidence of infection by multiresistant pseudomonads or acinetobacter. We may only have one β-lactam that’s effective. There are studies on the prophylactic use of aerosolized colistin as an adjunct for treating the multiresistant Gram-negative infections.1–4 There’s a study from Britain5 (I didn’t think it could happen) in which they documented an outbreak of colistin resistance due to Pseudomonas aeruginosa traced to prophylactic use of nebulized colistin—not for treatment, but for prophylaxis. Colistin-resistant pseudomonas—I didn’t think it could happen, but it has.

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Kollef: There is also a study by Sirvent et al,1 on head-injured patients, in which they gave 24 hours of a cephalosporin antibiotic to those patients who are primarily ventilated, which is probably as good as anything you can do to minimize or prevent early-onset pneumonia.

REFERENCE

Maki: Most of those patients, probably 60%, have aspirated on the scene with head injuries prior to admission.

Kollef: But the problem, I think, is that people look at that and then they use the drug for a prolonged period, so I guess when you say “using colistin for prophylaxis,” you would be looking at a very short period of treatment.

Maki: I want to emphasize that I am not advocating. I am raising it as a possible novel approach that deserves to be studied to see if it might have a role. Or maybe it shouldn’t be used? We don’t have a good handle on it. But I can tell you there is a lot of aerosolized colistin being used around the country. There is belief in this magic bullet for multiresistant Gram-negative rods. When we have no choice, with very resistant organisms, it is reasonable to use aerosolized colistin as a therapeutic adjunct. Will it be beneficial to prevent infection? That’s the question that needs to be answered.

Chastre: Coming back to the barrier precautions, do you think it’s possible to use, for example, gloves, if the unit is understaffed? In my experience, in many cases gloves are not used appropriately.

Maki: There’s quite a bit of evidence that gloves properly used would be beneficial. Something that’s not been appreciated and talked about is that if you handle a patient who is colonized with vancomycin-resistant-enterococcus or MRSA—most of these patients are colonized and have a lot of organisms on the skin surface, even away from the target site, such as the lung or a surgical wound or the urinary tract—as you take your gloves off, 30% of the time resistant organisms will get onto your hands in the mere process of removing your gloves. Hand hygiene procedure is essential after you remove your gloves. A lot of people think, “I used gloves. I don’t have to wash my hands; I don’t need to use hand hygiene.” And that’s a big mistake.

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