Antibiotic Stewardship in the Intensive Care Unit

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ABSTRACT

Antimicrobial stewardship encompasses the optimization of agent selection, dose, and duration leading to the best clinical outcome in the treatment or prevention of infection. Ideally, these goals are met while producing the fewest side effects and lowest risk for subsequent resistance. The concept of antimicrobial stewardship can be directly applied to the prescription of empirical antibiotic therapy in the intensive care unit (ICU) because it is well described that inappropriate initial regimens lead to increased mortality. As such, care should be taken to identify factors that place patients at risk for infection with pathogens demonstrating reduced susceptibility or multidrug resistance. Research efforts have concentrated on molecular diagnostic techniques to aid in more rapid organism detection and thus potential for earlier therapy appropriateness and deescalation, although limitations prohibiting widespread implementation of this technology exist. Also of great importance with regard to stewardship efforts is infection prevention. Effective prophylactic strategies reduce the occurrence of nosocomial infections and may therefore improve patient outcomes while obviating the need for otherwise necessary antimicrobial exposure.

KEYWORDS: Antibiotic stewardship, infection, intensive care unit

IMPORTANCE OF INITIAL APPROPRIATE ANTIMICROBIAL THERAPY

In 1999, a prospective evaluation of 2000 consecutive patients admitted to the medical and surgical ICUs at Barnes-Jewish Hospital was published.2 Among those individuals, 655 (32.8%) had a clinically recognized and microbiologically confirmed infection during their stay in intensive care. Of the infected patients, 169 (25.8%) received initially inappropriate antimicrobial treatment, defined as the absence of antimicrobial agents directed at a specific class of microorganism (eg, absence of therapy for Candida species isolated from blood cultures) or the administration of an antimicrobial agent to which the microorganism responsible for the infection was resistant.

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Inappropriate initial antimicrobial therapy for var-
ious infections has been reduced (Fig. 1).3–7 During the last decade several evolving factors have made the administration of appropriate initial antimicrobial therapy more difficult to achieve in the clinical setting. Foremost has been the increase of antimicrobial resistance among bacterial and nonbacterial pathogens.8 This is likely related to several factors, including the greater overall use of broad-spectrum antibiotics,9 much of which stems from the changing demographics of patients entering hospitals. Patients are generally older, more often immunosuppressed, and much more likely to have risk factors associated with health care exposure compared with a decade earlier.10 Patients with health care–associated risk factors appear to be the fastest-growing segment of the U.S. population requiring hospital admission for the treatment of serious infections. These risk factors include residence in a nursing home or long-term care facility, having a recent hospitalization for at least 2 days during the preceding year, attendance at a hemodialysis clinic or infusion center for the administration of chemotherapy or antibiotics, and having received hospital care at home (eg, intravenous therapy, wound care, specialized nursing care through a health care agency). The importance of categorizing patients as being at risk for a health care–associated infection is that the pathogens often causing these infections are nosocomial or health care–based pathogens [eg, methicillin-resistant Staphylococcus aureus (MRSA), Pseudomonas aeruginosa] instead of community pathogens (eg, Streptococcus pneumoniae, Haemophilus influenzae); thus they are at greater risk of receiving an inappropriate antibiotic treatment regimen. Additionally, the health care system has created areas outside of the hospital setting where multidrug-resistant bacteria are likely to emerge and from which they can spread into hospitals and the community. These areas include long-term care facilities for neurological rehabilitation, chronic mechanical ventilation, and posthospitalization care. Patients admitted to these facilities are often device laden (eg, tracheostomy, gastrostomy tube, urinary catheter, intravascular catheter) and repetitively exposed to antibiotics, creating a unique environment for resistance to emerge.

Despite increasing antimicrobial resistance from both gram-positive and gram-negative bacteria, there are few novel antimicrobial agents in development. Perhaps of equal concern are the insidious increases in the minimum inhibitory concentration (MIC) of currently available antibiotics required to kill specific bacteria. Unfortunately, many clinical microbiology laboratories do not test for and/or report MICs routinely, and clinicians are often unaware of the relative insensitivity of the clinical isolate to the prescribed drug class. This is of great consequence because the treatment of infections with antibiotics demonstrating susceptible yet elevated MICs has been linked to treatment failures and greater mortality.11–13

Several strategies can be applied to optimize initial antibiotic therapy. First, focused and dedicated efforts should be made to reduce, if not eliminate, preventable health care–associated infections as well as community-acquired infections through the use of validated infection control and vaccination programs. This is discussed in more detail later in the article. Second, the unnecessary use of antibiotics needs to be curtailed. This is a difficult global challenge because there are multiple clinical areas, both in the hospital and in outpatient settings, where antibiotics are prescribed by clinicians with varying degrees of expertise (or available for direct purchase by patients without health care provider input). Third, initial antibiotic selection should be based on recognition of the patient’s recent antibiotic history (or lack thereof), evaluation for prior infections with a drug-resistant pathogen, and an understanding of institutional or unit-specific antibiograms. Prior antibiotic use is clearly a risk factor for subsequent resistance,14,15 and in general reutilization should be avoided. Design of institution-specific treatment pathways for infections such as nosocomial pneumonia or severe sepsis should be based on local antibiograms in an attempt to optimize the likelihood of prescribing an initially appropriate
regimen. Within the protocol, recommendation of a combination therapy regimen (two or more antibiotics) targeting gram-negative pathogens should be made, focusing on patients with a risk factor profile as described or in patients cared for in hospitals or ICUs with a high baseline prevalence of antibiotic-resistant pathogens.\textsuperscript{16,17} The link between the prescription of combination therapy and initial appropriate therapy is clear, as is the association linking appropriate therapy and improved survival; however, direct comparisons of combination therapy to monotherapy generally demonstrate no difference with respect to mortality in populations with wide-ranging severities of illness.\textsuperscript{18-20} A plausible explanation for this is that comparative studies have excluded patients or have not controlled for patient risk for infection caused by antibiotic-resistant pathogens. A recent propensity-adjusted comparison of combination and monotherapy in patients with septic shock suggests a survival benefit with prescription of combination therapy.\textsuperscript{21} This finding may in part be a result of including patients that are more likely to be infected with antibiotic-resistant pathogens. The last component to providing optimal initial therapy is the prescription of antibiotic regimens with dosing schemes that target achievement of pharmacokinetic/pharmacodynamic (PK/PD) end points that have been linked to microbiological and clinical efficacy. PK/PD optimization is based on three concepts: (1) the duration of time the drug concentration remains above the MIC ($T_{\text{>MIC}}$), (2) the ratio of maximum drug concentration (peak concentration) to the MIC ($C_{\text{peak}}$/MIC), or (3) the 24-hour area under the curve to MIC ratio (AUC:MIC). Monotherapy regimens with conventional dosing strategies [oral administration or intermittent (30-minute) intravenous infusions] are likely to achieve the desired PK/PD end point in infections caused by a pathogen(s) with low MICs. However, organisms harboring elevated MICs jeopardize PK/PD target attainment with such regimens; consequently, alternative means to achieve these end points must be prescribed. The most logical method to achieve PK/PD target attainment is a dosage increase; however, this generally promotes intolerability and unacceptable toxic effects. In theory, combination therapy should improve the probability of meeting the desired PK/PD end point via additive PD interactions.\textsuperscript{22} The concept of extended duration infusions (antibiotic administered over 3 to 4 hours) or continuous infusions is not a novel concept with respect to optimizing PK/PD parameters, but one of great importance given this era of increasing pathogen MICs. Monte Carlo simulations suggest extended infusions will be of greatest benefit in patients that are infected with a pathogen which has an elevated MIC, demonstrate preserved renal function,\textsuperscript{23,24} or have altered volumes of drug distribution\textsuperscript{25} as commonly occurs in patients with sepsis or intraabdominal infection. The clinical impact of extended or continuous infusions has yet to be realized, which is likely not a failure of the science but the lack of study in patients that fulfill the characteristics where this dosing strategy will be of greatest benefit compared with traditional dosing regimens.\textsuperscript{26,27}

**EARLY PATHOGEN IDENTIFICATION FOLLOWING RAPID MOLECULAR DIAGNOSTIC TESTING**

As already discussed, the approach to infection in the ICU is often empirical in nature, with broad-spectrum antibiotics frequently employed to increase the likelihood of appropriate initial antibiotic selection. The ability to modify or deescalate therapy is dependent upon the results of microbiological diagnostic testing, and current approaches to identifying infection-causing pathogens are limited despite extensive clinical experience. Culture represents the most commonly employed method, but results are often unavailable for 24 to 72 hours or longer, with susceptibility testing requiring additional time. Culture integrity is dependent on proper technique, timing of obtaining, and lack of concurrent antibiotic administration.\textsuperscript{28} As expected, contaminated cultures have been associated not only with additional testing but also with prescription of unnecessary antimicrobials and increases in hospital costs.\textsuperscript{29} Complementary diagnostic methods are also flawed. Microscopy, serology, and antigen testing have been criticized due to their invasiveness, interpretation complexity, and high rate of false positivity.\textsuperscript{30} Given the inherent limitations of these strategies, research efforts have concentrated on molecular diagnostic approaches to be used adjunctively, or in place of, culture-based methods. Various techniques for pathogen detection have been described in the literature, but focus will be placed on peptide nucleic acid fluorescent in situ hybridization (PNA FISH) and polymerase chain reaction (PCR) and their influence on delivering more timely species identification. Employment of these strategies may ultimately lead to shorter time to appropriate antibiotics, antimicrobial deescalation, and potential cost savings in addition to minimization of antimicrobial resistance and adverse effect development. Table 1 provides a brief overview of both testing strategies.

**PNA FISH**

Enterococcal species are now the fourth most common organism to cause nosocomial bacteremia. In recent years, an increase in vancomycin-resistant \textit{E. faecium} isolates has been appreciated, with frequencies reported at 60%.\textsuperscript{31} Given this concerning trend, a before and after study enrolling 224 bacteremic patients over 2 consecutive years compared traditional identification methods of gram-positive cocci in pairs and chains to the PNA
FISH test for *E. faecalis* and other enterococci paired with an antimicrobial treatment algorithm. PNA FISH identified *E. faecium* and *E. faecalis* as the causative pathogen a median of 2.3 days (1.1 vs 3.4 days; *p* < 0.001) and 3 days (1.1 vs 4.1 days; *p* < 0.001) faster than customary methods, respectively. A significant decrease in the amount of time to initiation of appropriate antibiotics with PNA FISH was appreciated, primarily due to more rapid prescription of linezolid for vancomycin-resistant enterococcus (1.3 vs 3.1 days; *p* < 0.001). Furthermore, a significant reduction in mortality at 30 days was realized in the PNA FISH group (26% vs 45%; *p* = 0.04).  

PNA FISH technology has also been utilized in the identification of nonenterococcal gram-positive organisms, specifically to differentiate between *Staphylococcus aureus* and presumed culture contamination with coagulase-negative staphylococci, with the end goal of limiting inappropriate vancomycin usage. A retrospective evaluation of 223 episodes of bacteremia due to gram-positive cocci in clusters compared a study group with cultures found to be negative for *S. aureus* via PNA FISH testing to a control group whose blood samples did not undergo this analysis. A trend in the study group toward shorter median hospital length of stay (4 vs 6 days; *p* < 0.05, CI 0.95 to 1.87) and reduced hospital costs including bed, laboratory, and pharmacy expenses of approximately $4,000 was demonstrated in non-ICU patients. The analysis failed to show cost savings or decreases in length of stay in the ICU population, which may be due to the small ICU sample size (ICU control arm *n* = 7, ICU PNA FISH arm *n* = 12).  

With regard to gram-negative organisms, PNA probes exist to detect *Klebsiella pneumoniae*, *Escherichia coli*, *Acinetobacter spp.*, and *Pseudomonas aeruginosa*, but clinical outcomes data regarding these assays are lacking. In contrast, research surrounding the utility of PNA FISH implementation for the identification of *Candida* spp. has become more prevalent in keeping with contemporary shifts in the epidemiology of candidemia. *Candida albicans* remains the cause of more than 65% of invasive *Candida* infections, but of late *Candida glabrata* and *Candida krusei* have surfaced as important infection-causing pathogens. The growing rate of infections caused by such species has been particularly worrisome because *C. krusei* is intrinsically resistant to fluconazole, a commonly used agent for presumed candidemia, and *C. glabrata* displays dose-dependent fluconazole susceptibility with resistance reported in ~14 to 23% of isolates. As such, PNA FISH probes have been developed for the rapid differentiation between *C. albicans*, *C. glabrata*, and other yeast and have demonstrated accurate species identification in 1.5 to 3 hours after cultures are found to be positive. PNA FISH implementation in the setting of fungemia has been associated with approximately $1800 in cost savings per treated patient secondary to a decrease in echinocandin usage.

**Table 1** Overview of Select Molecular Diagnostic Techniques

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<thead>
<tr>
<th>Diagnostic Technique</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Peptide nucleic acid fluorescent in situ hybridization</td>
<td>• Utilization of fluorescent-labeled peptide nucleic acid probes targeting species-specific ribosomal RNA (PNA FISH) • No information provided on susceptibility or virulence factors • Uncomplicated assay • Identification within hours of blood culture positivity</td>
</tr>
<tr>
<td>Polymerase chain reaction (PCR)</td>
<td>• Detection and quantification of specific sequences in a DNA or RNA sample • Some provide select antimicrobial resistance data (ie, MSSA vs MRSA) • Results available within 1 to 24 hours, depending on the assay</td>
</tr>
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MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*.  

**PCR**  
Lehmann and colleagues assessed the adequacy and rapidity of antimicrobial therapy associated with multiplex PCR testing versus traditional blood culture in a retrospective cohort trial of 436 septic patients. The leading infection diagnoses included intraabdominal sepsis followed by nosocomial and community-acquired pneumonia. Blood culture identified 117 and PCR 154 clinically significant pathogens. The employment of PCR technology would theoretically have led to 107 fewer days of inappropriate therapy spread across all enrolled subjects. Approximately 36 days of gainable early adequate therapy for every 100 PCR tests performed in the ICU or surgical wards was appreciated; this effect was more profound in patients with intra-abdominal sepsis, nosocomial pneumonia, catheter-related sepsis, multiorgan failure, pyelonephritis, and neutropenic fever than other diagnoses (AOR [adjusted odds ratio] 3.9; CI 1.4 to 11.3).  

Discordance between blood culture and PCR findings was also demonstrated in a prospective, observational cohort trial comparing 42 severe sepsis and 63 surgical control patients; 34.7% of PCRs versus 16.5% of cultures are found to be positive. Interestingly, even when blood cultures failed to yield an organism, positive PCR findings
from septic patients correlated well with disease severity and host infection–related biomarker response.\textsuperscript{45}

PCR has also been utilized in the setting of staphylococcal bacteremia. In practice, decisions to de-escalate therapy from anti-MRSA antimicrobials to narrow-spectrum β-lactam antibiotics are often delayed pending the results of susceptibility testing. The issue of scaling back antibiotics is also confronted when awaiting speciation of staphylococcal species, namely \textit{S. aureus} versus presumed contaminant cultures growing coagulase-negative staphylococcus. These two common clinical scenarios prompted the development of an assay to detect \textit{S. aureus} and coagulase-negative staphylococci while simultaneously determining methicillin resistance directly from positive blood culture bottles. Recognizing that virtually all MRSA contain the \textit{mecA} gene, a triplex PCR assay was developed to target \textit{mecA} as well as the \textit{tuf} and \textit{nuc} genes, both of which are essential components of the \textit{S. aureus} bacterial genome. In an evaluation of 341 blood cultures positive with gram-positive cocci clusters, investigators demonstrated that results derived from the triplex PCR were congruent with those of traditional methods for \textit{tuf} (99.7%), \textit{nuc} (100.0%), and \textit{mecA} (99.1%), respectively. The PCR was also found to have a sensitivity and specificity of greater than 98% for all three genes. The entire procedure was completed in less than 90 minutes, showing significant potential for earlier reporting of microbiological findings.\textsuperscript{46}

A final area of importance to the critical care practitioner is the use of PCR technology in the diagnosis of \textit{Clostridium difficile} infection. Stool culture and cell cytotoxic assay remain the diagnostic gold standard, but most health care facilities now utilize the enzyme immunoassay because it can be completed within 2 hours, as opposed to 24 to 48 with the former methods. The immunoassay, however, is limited by its sensitivity, as up to 40% of positive cases may be missed. Investigators have demonstrated PCR sensitivity and specificity at 77.3% and 99.2%, respectively.\textsuperscript{47} PCR technology is further appealing because it is more sensitive in detecting \textit{C. difficile} than immunoassay (91.4% vs 66%, \(p < 0.0001\)) and takes the same minimal amount of time to perform.\textsuperscript{48}

\section*{Role of Molecular Diagnostic Methods in the ICU}

One of the most significant limitations to the implementation of molecular diagnostic testing is that the discussed assays detect only select prespecified pathogens. As mentioned earlier, the treatment of infection in the ICU is often empirical, and therapy is prescribed to cover a broad microorganism differential. As such, faster time to identification may not be realized if an assay is not designed to detect the infecting pathogen. The widespread use of these molecular diagnostic methods is further limited by the fact that, whereas some of the aforementioned methods are commercially available, others are “home grown” and therefore not widely obtainable. Furthermore, most of these tests still rely on positive blood culture findings prior to execution, therefore not diminishing the time delay due to culture incubation. Ultimately, more research is needed to determine whether implementation of these diagnostic tests will be followed by meaningful differences in clinical and economic outcomes prior to their standard employment in the ICU setting.

\section*{DEESCALATION STRATEGIES}

Recognizing that molecular diagnostic testing is not universally feasible, a discussion of alternate methods to facilitate antimicrobial deescalation is warranted. Deescalation refers to the modification of an empirical antimicrobial regimen to an alternate regimen with a narrower spectrum of activity. The majority of available literature describing ICU antimicrobial deescalation has been published on the ventilator-associated pneumonia (VAP) population. Because a thorough review of this topic has been previously published,\textsuperscript{49} focus will be placed on three recent studies, one evaluating VAP and two evaluating health care–associated pneumonia (HCAP).

Eachempati and colleagues evaluated 138 surgical ICU patients who developed VAP diagnosed by bronchoalveolar lavage for differences in recurrent pneumonia or mortality. Patients were categorized as receiving appropriate empirical therapy, antibiotic escalation, or deescalation therapy, as defined as either fewer or narrower-spectrum antibiotics as compared with the initial regimen. Antibiotics were deescalated at 48 to 72 hours when organism identification and susceptibility data were available. Empirical coverage for gram-negative infection was cycled monthly. The mean Acute Physiology and Chronic Health Evaluation (APACHE) III score was 82.7 points, and 70% of patients required vasopressor support. Ninety-three percent of patients received appropriate initial therapy, 8% antibiotic escalation, and 55% antimicrobial deescalation. Authors found no difference in recurrent pneumonia (27.3% vs 35.1%; \(p = 0.349\)) or mortality rates (33.8% vs 42.1%; \(p = 0.324\)) between those patients who did and those who did not receive deescalation therapy, respectively.\textsuperscript{50}

Deescalation therapy is complicated in the setting of HCAP because only one third of nonintubated patients provide adequate sputum samples, and of those patients, an even smaller percentage produce an infectious isolate. The joint Infectious Diseases Society of America (IDSA) and American Thoracic Society (ATS) guidelines\textsuperscript{51} fail to address this specific patient group, which prompted the study by Labelle and colleagues in which 870 patients with HCAP were evaluated in a retrospective cohort study, 439 (50.5%) of whom were
culture-negative. When compared with culture-negative patients, culture-positive patients were significantly more likely to receive appropriate initial antibiotic therapy (71.7% vs 15.4%, p < 0.001) as well as regimens that adhered to the ATS/IDSA nosocomial pneumonia guidelines (74.5% vs 15.4%, p < 0.001). Culture-positive patients were significantly more likely to undergo deescalation of their initial antimicrobial regimen than culture-negative patients (31.4% vs 20.7%, p = 0.016). Antimicrobial escalation was no different between groups (15.1% vs 14.7%, p = 0.872).52

Schlueter and colleagues have also published on this topic. They retrospectively evaluated 102 patients identified by use of a pneumonia order set, 72% of whom were culture-negative. Authors described deescalation occurring in 77% of the culture-positive and 75% of the culture-negative patients (p = 1.00), with the latter undergoing deescalation ~1 day earlier (3.93 vs 5.04 days; p = 0.03). The majority of culture-negative patients were deescalated to moxifloxacin, the institution’s formulary respiratory fluoroquinolone. Readmission rates did not differ between patients who did and did not undergo deescalation, although patients who may have been readmitted to other institutions were not captured.53

**PHARMACOLOGICAL INFECTION PREVENTION IN THE ICU**

Infection prevention strategies play an important role in antimicrobial stewardship because they can have significant impact on antibiotic utilization. Effective prevention strategies reduce the occurrence of nosocomial infections and may therefore improve patient outcomes while obviating the need for otherwise necessary antimicrobial exposure. However, many approaches to preventing infection involve the utilization of topical or systemic antimicrobials and therefore can account for significant antimicrobial use with potential implications for the development of antibiotic resistance. The prevention of nosocomial infections requires a multifaceted integration of both nonpharmacological and pharmacological strategies. Although nonpharmacological approaches are vital to infection prevention, a review of these practices is beyond the scope of this paper. This section will focus on recent literature and recommendations supporting the use of pharmacological prevention strategies to reduce the incidence of VAP and surgical site infections.

Three main strategies utilizing either or both topical and systemic antimicrobials have been investigated for their ability to prevent nosocomial infections in the ICU: selective decontamination of the digestive tract (SDD), selective oral decontamination (SOD), and oral application of topical antiseptics. The SDD approach generally includes application of topical antimicrobials (most commonly including polymyxin E, tobramycin, ± amphotericin B) to both the oropharynx and the stomach four times daily. This regimen often includes intravenous administration of either a second-generation cephalosporin or ciprofloxacin. SOD utilizes topical antimicrobials similar to the mix used in SDD that are applied only to the oropharynx.

Prospective clinical trials of SDD were first performed in the 1980s, and an abundance of literature has since accumulated, resulting in multiple meta-analyses (Table 2). A meta-analysis performed in 2001 reported a significant reduction in the incidence of VAP, but it was noted that the treatment effects were inversely related to the methodological quality of the included studies.55 Since that time, the results of three large, prospective, randomized, controlled trials of SDD have been published demonstrating a significant reduction in mortality in mixed medical/surgical ICU (n = 934),56 surgical and trauma ICU (n = 546),57 and burn patient populations (n = 107).58 It is important to note that in these three trials, the participating centers had strikingly low rates of antimicrobial resistance thus limiting the application of these findings to institutions with high rates of MRSA, VRE, and multidrug-resistant gram-negatives.

SOD is an alternative approach in which topical antimicrobials are applied only to the oropharynx, thereby limiting the systemic exposure and potential untoward effects. A recent meta-analysis including four trials of SOD (n = 1,098) failed to show a reduction in the incidence of VAP (RR 0.69, 95% CI 0.41 to 1.18, p = 0.18) or overall mortality (RR 0.94, 95% CI 0.73 to 1.21, p = 0.63).59

In 2009 de Smet and colleagues published the results of the largest prospective, randomized trial to date investigating the effects of SDD and SOD. This crossover study was performed in 13 ICUs in the Netherlands, randomizing a total of 5939 patients to one of three arms: SDD including 4 days of intravenous cefotaxime and topical tobramycin/colicin/amphotericin B applied to the oropharynx and stomach until ICU discharge; SOD including the same topical regimen used in SDD applied only to the oropharynx; or standard oropharyngeal care consisting of three to four washings per day with sterile water. The primary outcome of crude 28-day mortality was not significantly different in the SDD, SOD, and standard care groups (26.9%, 26.6%, and 27.5% of patients, respectively). However, after adjusting for minor differences in baseline characteristics between groups, the adjusted odds ratios for mortality in the SDD and SOD groups as compared with the standard care group were 0.86 (95% CI 0.74 to 0.99, p = 0.045) and 0.83 (95% CI 0.72 to 0.97, p = 0.02), respectively. Given that a benefit was observed in both the SDD and SOD groups, it appears that administration of intravenous cefotaxime in addition to enteral
<table>
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<tr>
<th>Ref No.</th>
<th>Patient Type</th>
<th>Decontamination Regimen</th>
<th>Outcomes</th>
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<tbody>
<tr>
<td>55</td>
<td>Surgical and medical ICU</td>
<td>0.5 g of oral paste applied to buccal cavity 4 × /day: 2% polymyxin E, 2% tobramycin, 2% amphotericin B + Administered via gastric tube 4 × /day: 100 mg polymyxin E, 80 mg tobramycin, 500 mg amphotericin B + Cefotaxime 1 g IV 4 × /day for first 4 days</td>
<td>ICU Mortality</td>
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<td>SDD 69/466 (15%) vs control 107/468 (23%); <em>p</em> = 0.002</td>
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<td>Hospital Mortality</td>
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<td>SDD 113/466 (24%) vs control 146/468 (31%); <em>p</em> = 0.02</td>
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<tr>
<td>56</td>
<td>Surgical and trauma ICU</td>
<td>Applied to both nostrils (1 mL), mouth (3 mL), and stomach (5 mL) every 6 hours: 50 mg polymyxin B and 80 mg gentamicin dissolved in 10 mL of sterile saline (vancomycin 125 mg added to mixture for patients with ARDS or immunosuppressive therapy) + Ciprofloxacin 400 mg IV every 12 hours for first 4 days</td>
<td>Acquired Infections</td>
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<td>SDD 91/265 vs placebo 149/262; <em>p</em> = 0.001</td>
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<td>ICU Mortality</td>
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<td>SDD 52/265 (20%) vs placebo 75/262 (29%); <em>p</em> = 0.132</td>
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<td>57</td>
<td>Severe burns</td>
<td>0.5 g of oral paste applied to oropharynx 4 × /day: 2% polymyxin E, 2% tobramycin, 2% amphotericin B + 10 mL solution via enteral tube 4 × /day containing: 100 mg polymyxin E, 100 mg tobramycin, 500 mg amphotericin B + Cefotaxime 1 g IV every 8 hours for first 4 days</td>
<td>Incidence of Pneumonia</td>
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<td>SDD 17.0 vs placebo 30.8 per 1000 ventilator-days; <em>p</em> = 0.03</td>
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<td>ICU Mortality</td>
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<td>SDD 5/53 (9%) vs placebo 15/54 (28%); Relative risk 0.25 (95% CI 0.08–0.76)</td>
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<tr>
<td>59</td>
<td>Surgical and medical ICU</td>
<td>SDD 0.5 g of oral paste applied to oropharynx 4 × /day: 2% polymyxin E, 2% tobramycin, 2% amphotericin B + Administered via gastric tube 4 × /day: 100 mg polymyxin E, 80 mg tobramycin, 500 mg amphotericin B + Cefotaxime 1 g IV 4 × /day for first 4 days</td>
<td>28-day Mortality</td>
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<td>SDD 546/2045 (26.9%) vs SOD 502/1904 (26.6%) vs SC 544/1990 (27.5%)</td>
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<tr>
<td></td>
<td>SOD</td>
<td>Unadjusted OR for SDD vs SC = 0.94 (95% CI 0.82–1.08)</td>
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<td>Unadjusted OR for SOD vs SC = 0.95 (95% CI 0.82–1.10)</td>
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<td>Adjusted OR for SDD vs SC = 0.83 (95% CI 0.72–0.97)</td>
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<td>Adjusted OR for SOD vs SC = 0.86 (95% CI 0.74–0.99)</td>
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ARDS, acute respiratory distress syndrome; ICU, intensive care unit; IV, intravenous; OR, odds ratio; SDD, selective digestive tract decontamination; SOD, selective oropharyngeal decontamination; SC, standard care.
Topical antimicrobials does not provide a survival benefit beyond that achieved with SOD alone. Although the percent of patients with at least one episode of bacteremia or candidemia was significantly reduced in the SDD and SOD groups, the incidence of VAP was not reported. Durations of mechanical ventilation, ICU and hospital lengths of stay, and antibiotic use were not different between the three groups.

A significant concern that has limited the application of SDD into clinical practice is the potential for selection of resistant organisms in individual patients as well as the long-term impact this could have on antimicrobial susceptibilities. In a prospective, randomized trial of SDD that was performed for 54 months, a shift toward colonization with gram-positive organisms was noted as was a significant increase in Staphylococcus aureus displaying methicillin resistance. Analysis of the collateral ecological effects incurred with SDD and SOD was assessed by the Netherlands study group using monthly point prevalence surveys of rectal and respiratory samples obtained before, during, and after the intervention periods. The main findings included an increase in the prevalence of gram-negative bacteria harboring ceftazidime resistance in the respiratory tract during SDD/SOD treatment. Additionally, upon discontinuation of SDD, a significant rebound effect on ceftazidime resistance, to levels above those identified preintervention, was observed in the intestinal tract isolates. Therefore it appears that development of resistance is a valid concern and that this may be particularly true for institutions with higher rates of drug-resistant pathogens, as has been previously reported.

Chlorhexidine (CHX) is the most extensively studied topical antiseptic for oral decontamination (Table 3). It demonstrates a broad-spectrum activity against many common VAP pathogens, including Pseudomonas aeruginosa, Acinetobacter species, and MRSA. It is noteworthy that numerous CHX concentrations (0.12%, 0.2%, and 2%), delivery vehicles (solution, paste, or gel), application frequencies (two to four times daily), and combinations of application sites (oropharyngeal surfaces with or without nasal surface administration) have been studied.

Cardiothoracic surgery patients constitute a large sample of the critically ill subjects in which CHX is most well described. Although all patients were mechanically ventilated in each of these trials, the total duration of mechanical ventilation was less than 24 hours in the overwhelming majority. Nonetheless, compared with placebo, CHX significantly reduced nosocomial infections and specifically lower respiratory tract infections by an absolute risk reduction of 6.5% in two separate studies.

The effect of CHX on the incidence and rate of VAP has also been studied in medical-surgical critically ill patients projected to have an ICU length of stay of 5 or more days and mechanical ventilation requirements exceeding 48 hours upon enrollment. The first notable

<table>
<thead>
<tr>
<th>Study Reference No.</th>
<th>Concentration</th>
<th>Vehicle</th>
<th>Frequency</th>
<th>Application Site</th>
<th>Patient Type</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>64</td>
<td>0.12%</td>
<td>Solution</td>
<td>2 × /day</td>
<td>Oropharyngeal</td>
<td>Cardiac surgery</td>
<td>LRTIs CHX 5/173 vs plb 17/180; p &lt; 0.05</td>
</tr>
<tr>
<td>65</td>
<td>0.12%</td>
<td>Solution Gel</td>
<td>4 × /day</td>
<td>Oropharyngeal nasal/oropharyngeal</td>
<td>Cardiac surgery</td>
<td>LRTIs CHX 45/485 vs plb 21/469; p = 0.002</td>
</tr>
<tr>
<td>66</td>
<td>0.2%</td>
<td>Gel</td>
<td>3 × /day</td>
<td>Dental/gingival</td>
<td>Medical surgical</td>
<td>Nosocomial infections: %/1000 ventilator-days CHX 10.7 vs plb 32.3; p &lt; 0.05</td>
</tr>
<tr>
<td>67</td>
<td>0.2%</td>
<td>Gel</td>
<td>3 × /day</td>
<td>Dental/gingival</td>
<td>Medical surgical</td>
<td>VAP CHX 13/114 vs plb 12/114; p = NS</td>
</tr>
<tr>
<td>68</td>
<td>0.2%</td>
<td>Solution</td>
<td>2 × /day</td>
<td>Oropharyngeal</td>
<td>Medical neurological</td>
<td>VAP CHX 14/88 vs plb 15/93; p = NS</td>
</tr>
<tr>
<td>69</td>
<td>2%</td>
<td>Gel</td>
<td>4 × /day</td>
<td>Buccal cavity</td>
<td>Medical surgical</td>
<td>VAP CHX 13/127 vs CHX/COL 16/128 vs plb 23/130; p &lt; 0.05</td>
</tr>
<tr>
<td>70</td>
<td>2%</td>
<td>Solution</td>
<td>2 × /day</td>
<td>Oropharyngeal</td>
<td>Medical surgical</td>
<td>VAP CHX 5/102 vs plb 12/105; p = NS</td>
</tr>
</tbody>
</table>

CHX, chlorhexidine; COL, colistin; LRTIs, lower respiratory tract infection; NS, not significant; plb, placebo; VAP, ventilator-associated pneumonia.
trial was a 60-patient pilot study of 0.2% CHX gel administered three times daily. The intent of the trial was to document a reduced occurrence of dental plaque colonization compared with placebo, a finding which was confirmed. Additionally, the incidence of VAP/1000 days of mechanical ventilation was significantly reduced in the CHX group compared with placebo (10.7% vs 32.3%, \( p < 0.05 \)). The same group of investigators later published a randomized, double-blind study comparing the same CHX intervention \( (n = 114) \) to placebo \( (n = 114) \). Overall, the combined primary end point (nosocomial bacteremia, bronchitis, or VAP) was similar between groups, a finding that held true when specifically examining the VAP outcomes (CHX 10.15% vs placebo 10.35%/1000 days mechanical ventilation).

An open-label, randomized trial compared 0.2% CHX \( (n = 224) \) applied twice daily to oropharyngeal surfaces to a 0.01% potassium permanganate control \( (n = 247) \) in a mixed cohort of medical-neurological ICU patients, of which approximately one third of patients required tracheal intubation. The primary end point, development of nosocomial pneumonia during the ICU stay, was no different between groups in the overall population (CHX 7.1% vs control 7.7%, \( p = 0.82 \)), nor in the subgroup of patients requiring mechanical ventilation (CHX 15.9% vs control 18.1%, \( p = 0.71 \)).

A randomized, double-blind study assigned patients to one of three groups including 2% CHX \( (n = 127) \), 2% CHX plus 2% colistin \( (n = 128) \), or placebo \( (n = 130) \), all formulated in a petroleum jelly by the study site pharmacies and applied to the oropharyngeal surfaces four times daily. The daily risk of VAP was reduced in both the 2% CHX group alone (hazard ratio 0.352; 95% CI 0.160 to 0.791; \( p = 0.012 \)) and in the 2% CHX/2% colistin group (hazard ratio 0.454; 95% CI 0.224 to 0.925; \( p = 0.030 \)) compared with placebo. It appeared the protective effect of the CHX groups occurred in the first 5 days after intubation (early VAP) and to a lesser extent in preventing late VAP.

Lastly, a randomized, but unblinded trial compared 2% CHX solution compounded by the study site pharmacy and a normal saline control applied to the oropharyngeal mucosa four times daily. Overall, the rate of VAP per 1000 ventilator days was reduced from 21 VAP episodes per 1000 ventilator-days in the control group to 7 in the CHX group \( (p = 0.04) \).

Although the individual trials have revealed inconsistent results, several meta-analyses have concluded that oral decontamination with antiseptics is associated with a lower risk of VAP. Unfortunately, each report combines cardiac surgery patients with medical-surgical patients and includes various CHX regimens, factors that severely limit the applicability of the results.

In summary, the current evidence for CHX yields conflicting results. CHX appears to most consistently reduce nosocomial infection rate overall in cardiac surgery patients. In the more diverse population of medical-surgical patients that receive prolonged mechanical ventilation, a distinct reduction in VAP incidence or rate has not been consistently observed. The trials that found a reduction in VAP used 2% CHX, a concentration not commercially available in the United States outside of surgical scrubs, and the benefit was mainly observed in the subgroup of patients developing VAP within the first 5 days of mechanical ventilation.

**SURGICAL SITE INFECTION PROPHYLAXIS**

Surgical site infections are a leading cause of nosocomial infection and are associated with significantly increased morbidity, mortality, and health care costs. Given the scope of this problem, in 2002 the Center for Medicare and Medicaid Services (CMS) worked in collaboration with the Center for Disease Control and Prevention (CDC) to establish the Surgical Infection Prevention (SIP) project, with the goal of promoting appropriate antimicrobial prophylaxis to reduce surgical site infections. SIP is now part of a broader mission titled the Surgical Care Improvement Project (SCIP), which addresses multiple components of care for the surgical patient, including infection prevention. Through the SIP project, experts reviewed the available evidence and guidelines and subsequently identified three process of care measures involving antimicrobial prophylaxis as focal points for improvement: (1) the proportion of patients who have parenteral antimicrobial prophylaxis started within 1 hour of incision (2 hours for vancomycin), (2) the proportion of patients who receive a prophylactic antimicrobial consistent with published guidelines, and (3) the proportion of patients who have antimicrobial prophylaxis discontinued within 24 hours of the end of surgery. These three objectives align with the goals of antimicrobial stewardship, to foster appropriate use of antimicrobials that optimizes patient outcomes while limiting the potential for misuse and development of resistance. For the purposes of national surveillance, five types of surgery (open-chest cardiac surgery excluding transplantation, vascular surgery, colorectal surgery, hip and knee arthroplasty excluding revisions, and abdominal or vaginal hysterectomy) are focused on, but these principles can be applied to a majority of surgical disciplines.

One large investigation of antimicrobial prophylaxis including 34,133 Medicare patients undergoing major surgery demonstrated that there is vast room for improvement. In this analysis, only 56% of patients received an antimicrobial agent within 1 hour prior to incision and antimicrobial prophylaxis was extended beyond 24 hours in 60% of patients. Working to achieve
these goals is critical because inappropriate timing is known to result in significantly reduced efficacy, and multiple reports indicate that extended antimicrobial prophylaxis is associated with increased occurrence of colonization and infection with resistant microorganisms. Furthermore, quality improvement studies have demonstrated that simple interventions can increase appropriate antimicrobial prophylaxis and reverse worrisome trends in antibiotic resistance. These findings highlight the importance of including antimicrobial prophylaxis for surgery in a comprehensive approach to antimicrobial stewardship.

CONCLUSIONS

 Provision of adequate antimicrobial therapy is often a challenge due to an increasing incidence of resistance and the paucity of new antibiotic agents in development. Focus should be placed on addressing patient-specific risk factors for health care–associated infection and treating accordingly with antimicrobial regimens tailored to address local resistance patterns and optimize PK/PD parameters. When possible, therapy should be deescalated to minimize the development of antimicrobial resistance and side effects experienced by the patient, although the role of molecular diagnostic methods in this process is still unclear. Prudent infection control practices are imperative, and when executed consistently they can prevent hospital-acquired infection and thus the need for otherwise required antibiotic therapy.

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