Evidence vs Instinct for Pneumonia Prevention in Hospitalized Patients

Michael Klompas[1,2]

[1]Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, and [2]Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts

(See the Major Article by Roquilly et al on pages 64–75.)

Over the years, literally dozens of interventions have been proposed to prevent hospital-acquired pneumonia. Most hospitals have combined a subset of these practices into "ventilator bundles" that are mandatory for all mechanically ventilated patients and sometimes all critically ill patients. Typical bundle elements include elevation of the head of the bed, routine oral care with chlorhexidine, daily sedative interruptions, daily assessment of readiness to extubate, deep venous thrombosis prophylaxis, and stress ulcer prophylaxis. Bundles vary broadly, however, from hospital to hospital [1].

Despite the popularity and broad penetration of ventilator bundles, the evidence supporting each bundle component is highly variable. Some components,

such as routine sedative interruptions and daily assessments of readiness to extubate, have been well studied and consistently associated with better outcomes [2–5]. Other components, such as head-of-bed elevation, have only been assessed in few patients [6, 7]. Finally, there are many successful interventions to prevent pneumonia that are not part of most hospitals' bundles [8].

A systematic review and meta-analysis in this issue of *Clinical Infectious Diseases* helpfully summarizes some of the vast literature on preventing hospital-acquired pneumonia and provides some clarity about the relative value of different interventions. Roquilly and colleagues identified 157 randomized controlled trials evaluating more than 20 different interventions. They conducted a series of meta-analyses to determine the impact of each intervention. The investigators selected hospital mortality as their primary outcome rather than hospital-acquired pneumonia. Of the 20 interventions studied, the only measure associated with a decrease in hospital mortality was selective digestive decontamination with regimens that included systemic antimicrobials (relative risk, 0.78, 95% confidence interval, .69–.89). Patient positioning, subglottic secretion drainage, closed suctioning systems, probiotics, early tracheotomy, early enteral feeding, stress ulcer prophylaxis,

silver-coated endotracheal tubes, oral decontamination with antiseptics or antibiotics, selective digestive decontamination without systemic antimicrobial therapy, and all the other interventions studied had no impact on mortality.

These provocative findings are a shot over the bow of infection prevention and quality improvement programs. This meta-analysis simultaneously challenges the validity of current ventilator bundles and begs the question why selective digestive decontamination with systemic antimicrobials is not routinely employed?

In truth, evidence has been gathering for years that the classic ventilator bundle merits revision. Some bundle components, such as stress ulcer prophylaxis, paradoxically increase pneumonia risk [9]. Other bundle components, such as routine oral care with chlorhexidine, do not clearly prevent ventilator-associated pneumonia and may even increase mortality risk [10, 11].

A major challenge in pneumonia prevention science is the subjectivity and poor specificity of clinical criteria to define pneumonia [12, 13]. Subjectivity allows for the possibility that lower pneumonia rates in the treatment arms of open-label studies are due to observer bias. Poor specificity allows for the possibility that some of the decreases in pneumonia rates in both open-label and

double-blind studies are due to less colonization rather than less pneumonia [14].

These challenges are the reasons why Roquilly and colleagues selected mortality as their primary outcome rather than hospital-acquired pneumonia. Other workers have reached similar conclusions [14–16]. Indeed, the Society of Healthcare Epidemiologists of America and Infectious Disease Society of America's latest revision of their compendium of strategies to prevent ventilator-associated pneumonia specifically prioritizes interventions associated with less time to extubation, shorter intensive care stays, lower hospital mortality, less antibiotic prescribing, and/or lower costs over interventions associated with lower ventilator-associated pneumonia rates alone [17]. The compendium recommends using noninvasive mechanical ventilation whenever possible, minimizing sedation, interrupting sedatives and assessing readiness to extubate daily, mobilizing patients early, using endotracheal tubes with subglottic secretion drainage, changing ventilator circuits only if visibly soiled or malfunctioning, and elevating the head of the bed.

This bundle of recommendations is different and more extensive than those suggested by the meta-analysis by Roquilly and colleagues. There are 2 reasons for this. First, the compendium authors evaluated some interventions that were not considered by Roquilly and colleagues such as noninvasive positive pressure ventilation, minimizing sedation, daily sedative interruptions, and daily assessment of readiness to extubate. Second, the compendium authors found merit in interventions associated with less time to extubation, shorter lengths-of-stay, less antibiotic prescribing, and/or lower costs in addition to those associated with lower mortality rates. This is important, partly because these are additional clinically meaningful outcomes, and partly because the amount of evidence supporting different interventions varies considerably. Some interventions, such as oral and digestive decontamination,

have been studied in literally tens of thousands of patients whereas other interventions, such as elevating the head of the bed, have only been studied in a few hundred patients. Most small studies lack adequate power to detect changes in mortality rates but can sometimes show positive effects on other outcomes.

Most strikingly, however, despite acknowledging that selective digestive decontamination is one of the only pneumonia prevention practice associated with lower mortality rates, the compendium authors downgraded this measure to a "special practice." Special practices are recommended only for units with persistently high ventilator-associated pneumonia rates despite high rates of adherence to the strategies suggested above. In doing so, the compendium authors echoed the concerns of many North American practitioners who fear that widespread use of antibiotics for digestive decontamination will ultimately increase antibiotic resistance and *Clostridium difficile* infections, particularly in North American hospitals where drug resistance is more prevalent than in Northern Europe. These practitioners fear that the deleterious consequences of multidrug resistance will ultimately outweigh any short-term mortality gain associated with digestive decontamination.

And indeed, resistome analyses of the gut flora of individual patients assigned to digestive decontamination do reveal progressive selection for antimicrobial resistance [18, 19]. At the population level, however, the data on resistance are more ambiguous. A recent meta-analysis of 35 studies found no difference between decontamination patients and control patients in the frequency of colonization or infection with methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci, aminoglycoside-resistant Gram-negative bacilli, or fluoroquinolone-resistant Gram-negative bacilli [20]. Remarkably, decontamination was associated with *less* Gram-negative bacilli resistant to third-generation cephalosporins or polymyxins.

These findings fly in the face of ecological studies associating greater antibiotic prescribing with greater rates of antibiotic resistance [21, 22]. Multiple explanations have been proposed [20]. Some suggest that lowering infection rates overall may decrease the absolute incidence of drug-resistant infections even if the proportion of drug-resistant pathogens may be higher. Others have noted that in many studies (but not all) patients randomized to decontamination ended up receiving fewer antibiotics in total compared to control patients perhaps because there were fewer new infections to treat.

A recurring critique of the decontamination literature is that most studies only followed a limited number of patients for a limited period of time. Observational data are now accruing, however, that the mortality benefit of digestive decontamination may be sustained and that low rates of antibiotic resistance can persist for years [23, 24].

As an infectious disease physician, I am instinctively uncomfortable with digestive decontamination with systemic antimicrobials. I focus much of my clinical work and teaching on encouraging clinicians to use antimicrobials as judiciously as possible. Nonetheless, we cannot ignore the accumulating evidence on digestive decontamination. There are precious few interventions in critical care associated with a 22% mortality reduction. And we must admit that there are other areas of infectious disease practice where we've come to accept routine antimicrobial prophylaxis (eg, bone marrow transplants, surgical prophylaxis, human immunodeficiency virus with low CD4 counts). It behooves us now to conduct the definitive studies of digestive decontamination in North America with long-enough follow-up periods to settle the question for once and for all of the relative benefits and risks of routine digestive decontamination. We owe it to our patients.

Note

The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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