In the Literature

**Oral Chlorhexidine to Prevent Ventilator-Associated Pneumonia (VAP)**


Most cases of pneumonia, including cases of VAP, are believed to be caused by organisms that initially colonize the oropharynx. Decontamination of the oropharynx has been suggested as a means to prevent VAP, but the use of antibiotics for this purpose raises concerns about the selection of organisms resistant to the agents used.

In a double-blind, multicenter Dutch trial, nonimmunocompromised adults who required mechanical ventilation for at least 48 h were randomly assigned to one of the treatment arms: chlorhexidine 2% in petroleum jelly FNA (the chlorhexidine group), chlorhexidine 2% plus colistin 2% in petroleum jelly FNA (the CHX/COL group), and placebo (petroleum jelly FNA alone). The standard of care at all participating intensive care units included a semirecumbent position, with the head of the bed elevated 30°. The trial utilized sequential survival analysis and was discontinued when a predetermined difference between treatment arms was reached.

Fifty-two (13.5%) of the 385 randomized patients developed VAP, including 13 (10%) of those assigned to the chlorhexidine group, 16 (13%) in the CHX/COL group, and 23 (18%) assigned placebo ($P = .012$). Neither mortality nor the number of days of mechanical ventilation were significantly affected. Although no statistically significant difference was achieved at earlier or later time points, endotracheal colonization during days 5–8 was significantly lower in the CHX/COL group, compared with each of the other 2 treatment groups, predominantly as the result of a reduction in prevalence of recovery of gram-negative bacteria. Similarly, although chlorhexidine application was associated with a reduction in oropharyngeal colonization with gram-positive organisms, CHX/COL reduced colonization at this site with gram-negative organisms as well.

The use of oral decontamination with chlorhexidine is a low-cost intervention that does not carry with it the risk of development of significant antibiotic resistance (although chlorhexidine can induce the expression of multidrug efflux pumps in *Pseudomonas aeruginosa*). But does it reduce the incidence of VAP? A recent meta-analysis failed to find evidence of a significant reduction in VAP or of mortality in association with the use of oral decontamination with chlorhexidine [1]. The study by Koeman and colleagues is suggestive of a beneficial effect, but is clearly not definitive. A number of issues can be raised regarding this study. The incidence of VAP among these patients was high by many current standards, and this may have been the result of overdiagnosis. The diagnosis of VAP in this study could be made on purely radiographic and clinical grounds. In fact, the mean clinical pulmonary infection score ($\pm$ SD) at the time of diagnosis was only $6.2 \pm 1.5$, indicating that many patients had very low scores and were therefore less likely to actually have pulmonary infection. Nonetheless, whatever the real benefit of chlorhexidine mouth care is (or is not) in the prevention of VAP, this inexpensive intervention is being widely adopted.

**Reference**


**Community-Acquired Pneumonia (CAP) and Coccidioidomycosis in an Area of Endemicity**


It is estimated that symptomatic coccidioidomycosis is likely to affect ~30,000 individuals each year in Arizona. Despite this estimate, only ~2000 cases were reported to the state’s Department of Health Services annually during 1998–2001. Valdivia and colleagues have now attempted to determine which of these numbers is closer to the truth by prospectively evaluating adults with CAP who presented to 3 primary care sites in Tucson, Arizona. Recruitment was conducted during 2 time periods: from 1 December 2003 through 21 February 2004, and from 1 May 2004 through 14 August 2004. The diagnosis was based on the use of several different serological tests for both IgG and IgM antibody to coccidoidal antigens.

Most patients (87%) were non-Hispanic white persons. A serological diagnosis of acute primary coccidioidomycosis (valley fever) was made in 16 (29%) of 55 patients with CAP (95% CI, 16%–44%). The only significant difference between those whose CAP was due to coccidioidomycosis and those whose CAP had a different etiology was a shorter residence time in the area of endemicity, which increased the likelihood of this endemic fungal infection. Patients with coccidioidomycosis were more likely to report myalgia and reduced productivity.

Antimicrobials were prescribed to 46
(84%) of the patients; 13 patients received 2 courses, and 1 received 3 courses of antibiotics. Patients with and without coccidioidomycosis were equally likely to receive antibiotics, including multiple courses. Only 1 patient received antifungal chemotherapy. All patients were improved when reevaluated after 6 months; none had been hospitalized.

These results confirm previous estimates of the remarkable frequency of coccidioidomycosis as a cause of febrile respiratory illness in southern Arizona. They nonetheless likely represent an underestimation for several reasons, including the fact that many individuals were tested during the first week of illness, when seroconversion may not yet have occurred. Furthermore, many patients with symptomatic primary coccidioidal infection may not seek medical care.

No clinical features allowed clinicians to distinguish acute coccidioidomycosis from bacterial or viral pneumonia, making the diagnosis dependent upon laboratory studies. The diagnosis therefore depends on an adequate level of suspicion and the convenient availability of tests with rapid turnaround times. The finding of this high frequency of coccidioidal infection among patients with CAP in this area of endemcity, together with the extensive and futile administration of unnecessary antibiotics, makes it clear that physicians should maintain a high level of suspicion and that, in areas of nonendemicity, a travel history which was also detected in 3 daptomycin-resistant S. aureus isolates recovered from patients whose bacteremia persisted in the face of daptomycin therapy, as well as other individual case reports of the emergence of resistance during therapy, provide an early warning regarding the emergence of daptomycin resistance. The mechanism of this resistance has not previously been defined.

Friedman and colleagues generated isolates with decreased susceptibility to daptomycin by serial passage of S. aureus MW2 in progressively higher concentrations of the antibiotic. Gradual increases in the MIC were noted over 20 daily passages, such that final values ranged from 3 to 20 μg/mL, having started at 0.75 μg/mL. Examination of these isolates by comparative genome sequencing identified 3 nonsynonymous single-point mutations in association with daptomycin resistance. The proteins affected were 2 subunit proteins of RNA polymerase, a histidine kinase sensor, and the lysylphosphatidylglycerol synthetase, MprF. The MprF mutant, which was also detected in 3 daptomycin-nonsusceptible clinical S. aureus isolates, was the first to appear in vitro, correlating with the first increase in daptomycin MIC.

The MprF protein contributes to the net positive charge of the surface envelope of S. aureus by altering membrane phosphatidylglycerol. The positive charge is critical to the interaction of the net negatively charged daptomycin with the bacterial cell membrane. Loss of function mutations in mprF would thus be expected to lead to reduced susceptibility to this antibiotic. Of interest, however, is that inactivation of mprF is associated with reduced virulence and increased susceptibility to cationic antimicrobial peptides [1]. Thus, the evidence suggests that a key step in the development of resistance to daptomycin is mutation in mprF but that other mechanisms are likely to contribute. It has been reported that preexposure of S. aureus to vancomycin may lead not only to reduced susceptibility to vancomycin, but also to reduced susceptibility to daptomycin because of the inability of this large molecule to penetrate through the thickened cell wall of organisms with the vancomycin-intermediate S. aureus phenotype [2]. Also of note is the high frequency of soil organisms capable of inactivating daptomycin via an as-yet unknown mechanism that may prove a harbinger of resistance in future clinical isolates [3].

References

Treatment of Chronic Chagas Disease

Five hundred sixty-six patients with serological evidence of Chagas disease that was not in the acute stage and who had no evidence of heart failure were assigned to open-label treatment on an alternating-sequence basis. Patients received benznidazole for 30 days or no treatment. Evaluation after a mean duration of follow-up of 9.8 years found that benznidazole treatment was associated with a lower likelihood of disease progression (adjusted hazard ratio, 0.24; 95% CI, 0.10–0.59) and a lower risk of developing electrocardiographic abnormalities.