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INSIDE

Penicillin vs Cephalosporin for Strep Throat—Which Is Better?

ABSTRACT & COMMENTARY

Synopsis: *Bacteriologic and clinical failures in adults with* Streptococcal tonsillopharyngitis *are twice as likely with oral penicillin therapy as with cephalosporin treatment. But, what is the significance of this finding?*

Source: Casey JR, et al. Meta-analysis of Cephalosporins vs Penicillin for Treatment of Group A Streptococcal Tonsillopharyngitis in Adults. *Clin Infect Dis.* 2004;38:1526-1534.

In the 28 years since G. V. Glass described the meta-analysis concept, countless meta-analyses have been published in the medical literature. In the present study, penicillin is compared with cephalosporins for the treatment of adults with group A ß-hemolytic streptococcal (GABHS) tonsillopharyngitis.

Casey and colleagues critically reviewed all randomized, controlled therapy trials performed in patients 12 or more years old with streptococcal sore throat. Treatment consisted of an orally administered antibiotic for 10 days. Bacteriologic cure (defined as absence of GABHS in a post-treatment throat culture) and clinical cure (defined as "resolution or improvement" of signs and symptoms) were tabulated. Multiple statistical manipulations analyzed the effects of 1) lack of double-blinding, 2) inferior methodologic quality, 3) uncertainty concerning compliance, 4) failure to account for pharyngeal streptococcal carriage, and several other study design weaknesses.

Of 66 randomized clinical trials that were reviewed, 57 were excluded because of such analytic problems as predominance of children over adults in the patient population, failure to separate adult data from those of children, poorly defined cure rates, and inadequate duration of antibiotic treatment (< 10 days). The remaining studies included treatment with loracarbef (3 studies), cefadroxil and cefdinir (2 studies each), and cefpodoxime and cefetamet (1 each). Penicillin V was the comparator penicillin compound.

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Analysis of all 2113 patients in 9 studies demonstrated an overall or summary odds ratio (OR) for bacterial cure of 1.83, thereby favoring cephalosporin treatment (an OR greater than 1 denotes a higher cure rate with cephalosporin therapy). For clinical cure, the OR was 2.29, again favoring cephalosporin over penicillin. Results were similar when sensitivity analysis parsed trials grouped by double-blinding, exclusion of carriers, trials deemed to be of high quality, and other methodologic measures. Stratified analysis, in which cephalosporins were analyzed individually and as generation groups (first-generation, second-generation, and so on), demonstrated both bacterial and clinical cure rate superiority in most cases, with the exception of clinical cure rate equivalence with loracarbef.

Although Casey and colleagues did not explicitly provide absolute overall cure rates, calculations from their data indicate that, in the 9 trials that were analyzed, bacteriologic and clinical cure rates of 92.4% and 95.3%, respectively, were found in cephalosporin-treated adult patients, compared with rates of 86.9% and 89.9% in penicillin-treated patients. Casey et al stated that 19 patients would need to be treated with a cephalosporin to result in 1 additional bacteriologic cure, were penicillin used instead. A similar benefit ratio results if one calculates a clinical cure estimate.

COMMENT BY JERRY D. SMILACK, MD

Readers of this article are left with the impression that an oral cephalosporin is the drug of choice for treatment of adults with GABHS tonsillopharyngitis. Before taking this statement at face value, *Infectious Disease Alert* readers would be well advised to peruse Dr. Alan Bisno's editorial commentary (*Clin Infect Dis*. 2004;38:1535-1537) that accompanies Casey et al's meta-analysis. Bisno takes issue with the latter's conclusions by citing several important caveats. First, some of the reports included in the meta-analysis had "appreciable deficiencies" (such as issues of compliance, timing of follow-up cultures, and inclusion of GABHS carriers), flaws that "are not likely to be overcome by even the most rigorous analytic statistical techniques." Second, because GABHS tonsillopharyngitis is usually a self-limited disease for which antibiotic therapy may shorten the course by only 1 or 2 days, assessing the importance of small differences in clinical cure rates is problematic. Third, if penicillin therapy leads to significant failure rates, why have we not seen reports of increased disease-associated or post-streptococcal complications?

Bisno concludes by asking whether a small difference in bacteriologic and clinical cure rates—even if such a difference truly exists—really makes a clinically significant difference. He answers the question by saying that it doesn't, and that penicillin remains the drug of choice for treatment of adults with streptococcal tonsillopharyngitis. ■

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Time to Get Cereus!

ABSTRACT & COMMENTARY

Synopsis: *A patient with a disease resembling anthrax led to the identification of anthrax-like virulence factors in an isolate of* Bacillus cereus.

Source: Hoffmaster AR, et al. Identification of Anthrax Toxin Genes in a *Bacillus cereus* Associated with an Illness Resembling Inhalation Anthrax. *Proc Natl Acad Sci USA.* 2004;101:8449-8454.

A previously healthy patient presented with a 2-day history of nausea, vomiting, hemoptysis, short-

ness of breath, and fever. His chest X-ray was abnormal, and his WBC on admission was 12,000/mm^3, subsequently rising to a peak of 22,400/mm^3. Cultures of sputum and of blood yielded a Gram-positive bacillus identified using traditional phenotypic characteristics, including biochemical reactions, as *Bacillus cereus*. The patient required mechanical ventilation for 44 days, but eventually recovered.

Sequencing of the organism's 16S rRNA confirmed its identity as *B. cereus* while multilocus sequence typing found that it was closely related to, but distinct from, *Bacillus anthracis*. The patient's isolate, however, contained a circular plasmid, named by Hoffmaster and colleagues as pBCXO1, that had 99.6% similarity with the *B. anthracis* toxin-encoding plasmid, pXO1. In addition, a polysaccharide capsule cluster was encoded on a second plasmid, pBX218, thus providing an analog to the *B. anthracis* capsule genes encoded on its other plasmid, pXO2. The virulence of the patient isolate was confirmed by mouse inoculation experiments.

COMMENT BY STAN DERESINSKI, MD

B. cereus, a cause of food poisoning, is an uncommon cause of invasive infection. These infections mostly occur in immunocompromised patients, and have included post-traumatic or post-cataract surgery endophthalmitis, prosthetic valve endocarditis, native valve endocarditis in injection drug users, and meningitis in neonates and hematopoietic stem cell recipients.[1] Other reported infections include those of cerebrospinal fluid shunts and of vascular access.

B. anthracis, on the other hand, is a highly virulent organism that causes potentially fatal disease regardless of precipitating events or immunocompromise. This virulence is the consequence of the presence of the expression of genes carried by 2 plasmids, pXO1 and pXO2, that encode the lethal toxin complex and the poly-g-D-glutamic acid capsule, respectively. The virulent *B. cereus,* isolated from the patient discussed here, had acquired a plasmid encoding the anthrax toxins and a second plasmid capable of encoding polysaccharide capsular material.

As indicated by Hoffmaster et al, in a comment on the evolutionary plasticity of the microbial world, "depending on the number extent of lateral gene transfer, nature could produce an unlimited number of variations and combinations." Thus, when using standard clinical laboratory techniques, notions such as "anthrax bad, cereus not so bad" are potentially dangerous over simplifications that may have a number of important clinical and other implications, and that potentially apply to other organisms. Thus, in some instances, the identification of an isolate such as *B. cereus* may lead to its being inappropriately disregarded as a contaminant. The lack of association of severe virulence with such an isolate, may lead to unnecessary searches for other etiologies of a patient's perilous clinical state. Finally, an engineered bioterrorism agent that clinical laboratories identify simply as *B. cereus* could lead to significant delay in the identification of a sinister attack. ■

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Blood Cultures 2004

ABSTRACT & COMMENTARY

Synopsis: *A retrospective review has resulted in revision of recommendations for optimal methods of blood culturing in adults.*

Source: Cockerill FR III, et al. Optimal Testing Parameters for Blood Cultures. *Clin Infect Dis.* 2004;38:1724-1730.

COCKERILL AND COLLEAGUES EXAMINED THE EFFECTS of the volume of blood, the number of consecutive blood culture specimens, and the incubation time on the recovery of pathogens from 37,568 blood cultures obtained from adults. The study was performed at the Rochester, MN Mayo Clinic from 1996 to 1997, and used the automated BACTEC 9240 instrument. For each culture, 20 mL of blood was split equally into a BACTEC Plus aerobic/F resin bottle and a BACTEC Lytic/10 Anaerobic/F bottle, which were then automatically examined for a fluorescent marker every 10 minutes. The bottles contain enriched soybean-casein digest broth.

Pathogen recovery increased with increasing volume of blood cultured up to 40 mL in patients who did not have endocarditis. As the number of consecutive blood cultures over 24 hours increased to > 2, the relative yield increased. Among patients without endocarditis, the first positive blood culture, when more than 1 was obtained, came on the first specimen in 77%, on the second in 18%, the third in 3.9%, and the fourth in 1.1%. Among patients with endocarditis, with 2 or more cultures, the first positive was the first sample in 91.2%, the second in 5.9%, the third in none, and the fourth in 2.9%.

Among patients without endocarditis, all bacteremias were detected within 6 days, with 99.5% within 5 days of incubation. All bacteremias in patients with endocarditis were detected within 5 days. Of interest, 100%

of *Streptococcus pneumoniae* were detected within 24 hours and, all enterococci were recovered within 96 hours. Two isolates of *Cryptococcus neoformans,* and 1 of *Candida albicans,* required more than 6 days for recovery.

COMMENT BY STAN DERESINSKI, MD, FACP

As Cockerill et al point out, based on limited data using manual blood culture methods, it has been widely accepted that 2 to 3 consecutive blood specimens be obtained for culture over a 24-hour period, from patients in whom bacteremia is suspected. The greater sensitivity of the automated blood culture system used here, when compared to manual systems, would suggest that fewer cultures would prove necessary, but this did not prove to be the case. It may, however, be this greater sensitivity that paradoxically led to failure of this to prove true, since it may lead to a greater likelihood of detection of low level bacteremia, particularly in patient already receiving antibiotics.

These results may differ with use of other blood culture systems, as well as with other variations in methodology. For instance, some laboratories prefer to inoculate 2 aerobic bottles for cultures after the first in order to increase the recovery of organisms that grow poorly in an anaerobic environment. In addition, there may be indications for more prolonged incubation, as when organisms such as *Brucella* are suspected. It is of interest to note, that the identification of *Bartonella quintana* as the cause of bacteremia in homeless individuals was the result of blind acridine orange staining of apparently negative BACTEC blood culture bottles after 8 days of incubation.[1]

An aside: The use of automated blood culture systems is associated with greater rapidity of detection of bacteremia than the use of manual systems. This is only true, however, if a human being is available in the laboratory to respond appropriately. A recent study investigated blood cultures that first became positive at night when no microbiologists were present and at other times when they were present.[2] When none were present, it took 7 hours and 26 minutes to report results to a physician, and only 2 hours and 12 minutes when they were there. This greater than 5 hour difference could, in some cases, prove critical.

Cockerill et al make the following recommendations when using the BACTEC 9240 system for the detection of bacteremia in adults:

- 20 mL of blood should be obtained per venipuncture and distributed equally between an aerobic and an anaerobic blood culture bottle. This constitutes a single blood culture or blood culture set.
- At the time of the initial order within a 24-hour period, 2 20 mL blood samples should obtained, each by separate venipuncture.
- Two additional 20 mL samples should be obtained at separate intervals over the remaining 24-hour perio, as signs and symptoms of septicemia persist.
- Blood culture bottles should be incubated for 5 days.

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Pneumococcal Pneumonia—Bring Back the Microbiology Laboratory!

ABSTRACT & COMMENTARY

Synopsis: *When it is possible to obtain an adequate sputum specimen in a timely fashion, the sensitivities of Gram stain and culture in the diagnosis of pneumococcal pneumonia in bacteremic patients are high.*

Source: Musher DM, et al. Diagnostic Value of Microscopic Examination of Gram-Stained Sputum and Sputum Cultures in Patients with Bacteremic Pneumococcal Pneumonia. *Clin Infect Dis.* 2004;39:165-169.

Musher and colleagues in Houston examined the usefulness of examination of Gram-stained sputum specimens and of sputum culture for the diagnosis of pneumococcal pneumonia. They included all 105 patients with bacteremic pneumococcal pneumonia seen over 6 years at their VA hospital, and examined the results of the first sputum specimen submitted to the laboratory. A sputum specimen was adequate if there were at least 10 WBC for each epithelial cell. A positive sputum Gram stain (predominant Gram-positive cocci in pairs and chains) was detected in 33 (31%), and a positive culture in 46 (44%) of the patients. However, no sputum was submitted from 31 patients, and in 16, the sample was judged inadequate. When these cases are excluded from analysis, the sensitivity of the Gram stain was 57%, and that of culture was 79% (*see Table 1*).

Antibiotic therapy prior to specimen collection signif-

Table 1.

Sensitivity of Gram Stain and Culture in Bacteremic *Pneumococcal pneumonia*

	All Patients (105)	With Sputum Sample (74)	With Adequate Sputum Sample (58)
Gram Stain	31%	45%	57%
Culture	44%	62%	79%

•figures in parentheses represent number of patients

Table 2.

Sensitivity of Gram Stain and Culture in Bacteremic *Pneumococcal pneumonia* in 58 Patients with an Adequate Sputum Specimen

	Duration of Antibiotic Therapy Before Specimen Collection			
	> 24 hours (7)	6 to 24 hours (18)	< 6 hours (18)	No Antibiotic (15)
Gram Stain	14%	50%	61%	80%
Culture	29%	89%	78%	93%

•figures in parentheses represent number of patients

icantly decreased the sensitivities of both Gram stain and culture (*see Table 2*). The sensitivities of Gram stain and culture, when sputum was obtained prior to antibiotic administration, were 80% and 93%, respectively. There was a marked decrease in sensitivities when specimens were obtained 24 hours or more after the initiation of antibiotic therapy.

COMMENT BY STAN DERESINSKI, MD, FACP

A number of studies, many published in pulmonology journals, have reported that sputum Gram stain and culture are ineffective in the diagnosis of pneumococcal pneumonia. This has led to recommendations by organizations such as the American Thoracic Society, that attempts at microbiologic diagnosis not be performed in patients with community acquired pneumonia. As, however, pointed out by Musher et al, the studies upon which those recommendations were based, commonly included in their denominator patients, from whom no adequate sputum specimen was obtained. The current study demonstrates that sputum examination and culture are effective in the diagnosis of pneumococcal pneumonia and, if the specimen is obtained within a reasonable time after the initiation of antibiotic therapy, quite sensitive.

Since this study only examined patients with bacteremic pneumococcal pneumonia, it provides no information regarding the specificity of the Gram stain, nor does it examine its accuracy in the diagnosis of bacterial pneumonia of other etiology. Musher et al cite publications that suggest that Gram stain is even more effective in these diagnoses.

The current IDSA guidelines for treatment of community-acquired pneumonia call for the administration of a first dose of antibiotic within 4 hours of registration, a tactic associated with improved outcomes in hospitalized patients. Thus, the need to obtain an adequate sputum sample must not delay the initiation of empiric therapy beyond that time point. If an adequate specimen cannot be obtained before the first dose of antibiotic is given, Musher et al suggest that "microscopic evaluation of a Gram-stained sputum sample is likely to be useful within the first 6 to 12 hours of therapy, and a culture may provide useful data using a sputum sample obtained up to 24 hours after antimicrobial therapy has been begun." Although not discussed in this article, the urinary antigen test for *Streptococcus pneumoniae* may also be diagnostically useful. ■

Telithromycin Tablets (Ketek)

By William T. Elliott, MD, FACP, and James Chan, PharmD, PhD

THE FDA HAS APPROVED TELITHROMYCIN, THE FIRST ketolide antibiotic. Ketolides are semisynthetic derivatives of the macrolide erythromycin that have activity against a wide spectrum of respiratory bacterial pathogens including multi-drug resistant *Streptococcus pneumoniae*. Telithromycin, which is a once-a-day oral tablet, is marketed by Aventis as Ketek.

Indications

Telithromycin is approved for the treatment of acute bacterial exacerbation of chronic bronchitis caused by *Streptococcus pneumoniae*, *Haemophilus influenzae*, or *Moraxella catarrhalis*; acute bacterial sinusitis caused by *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, or *Staphylococcus aureus*; and community acquired pneumoniae (CAP) of mild to moderate severity caused by *Streptococcus pneumoniae* (including multi-drug resistant isolates), *Hemophilus influenzae*, *Moraxella catarrhalis*, *Chlamydophilia pneumoniae*, or *Mycoplasma pneumoniae*.[1]

Dosage

The recommended dose for acute bacterial exacerbation of chronic bronchitis or acute bacterial

sinusitis is 800 mg once daily for 5 days. The recommended dose for community-acquired pneumonia of mild-to-moderate severity is 800 mg once daily for 7 to 10 days. Telithromycin can be taken with or without food.[1]

Telithromycin is supplied as 400 mg tablets.

Potential Advantages

Telithromycin has shown in vitro activity and clinical efficacy against multi-drug resistant *S pneumoniae*.[1-6] It also appears to have low potential to select for or induce macrolide lincosamide streptogramin B (MLSb) resistance.

Potential Disadvantages

The most common side effects were diarrhea (13.3%) and nausea (8.1%). Telithromycin is a substrate and inhibitor of CYP 3A4. Potent inhibitors increase the bioavailability of telithromycin, and the bioavailability of certain substrates of CYP 3A4 (eg, simvastatin, midazolam) are increased. Telithromycin has the potential to prolong QTc, and should be avoided in patients at risk. Exacerbations of myasthenia gravis and visual disturbances (eg, blurred vision, diplopia, problems with accommodation) have been reported.[1] Strains of *S pneumonia,* resistant to telithromycin, have been demonstrated in vitro.[1]

COMMENTS

Telithromycin, while derived from erythromycin, has higher binding affinity to ribosomes than erythromycin. It is active with dose dependent bactericidal activity against common respiratory bacterial pathogens including atypical/intracellular pathogens and drug resistant strains of *S pneumoniae*. Concentrations exceeding the MIC90 are achieved in bronchial mucosa and epithelial lining fluid.[7] Clinical cure rates of telithromycin (800 mg daily) were comparable to comparators such as clarithromycin (1000 mg daily), trovafloxacin (200 mg daily), and amoxicillin (3000 mg daily) for community acquired pneumonia; amoxicillin/clavulanate (1500/375 mg daily) and cefuroxime axetil (500 mg daily) for acute bacterial sinusitis; and cefuroxime, amoxicillin/clavulanate, and clarithromycin for acute exacerbation of chronic bronchitis.[1,2] Clinical cure has also been reported in a limited number of infections caused by multi-drug resistant S pneumoniae. These include isolates resistant to 2 or more of the following: penicillin, 2nd generation cephalosporins, macrolides, tetracycline, and trimethoprim/sulfamethoxazole.[1] Overall clinical cure ranged from 85-91% in these resistant pathogens.[1,2] Bacterial eradication of erythromycin or penicillin resistant *S pneumonia* in CAP was 92% (67/73) for telithromycin compared to 70% (7/10) for pooled comparators.[2] Telithromycin is generally well tolerated with diarrhea and nausea as the most common side effects. Exacerbations of myasthenia gravis and visual disturbances have been reported. The cost of telithromycin was not available at the time of this review.

Clinical Implications

Epidemiologic data indicate that bacterial resistance to commonly used antibiotics such as penicillin and erythromycin is increasing.[8] Penicillin resistant *S pneumonia* represents over half the isolates in many regions of the United States, erythromycin-resistant strains ranges from 23-41%, and penicillin and erythromycin resistance ranges from 13-30%. Telithromcyin appears to be an effective antibiotic for these resistant bacteria. It must, however, be prescribed judiciously to minimize development of bacterial resistance as resistant strains have been demonstrated in vitro. ■

Dr. Elliott and Dr. Chan are editors of Internal Medicine Alert. This article was published in the May 2004 issue.

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Prevention of Ventilator-Associated Pneumonia

By Saadia R. Akhtar MD, MSc

Ventilator-associated pneumonia (VAP) is nosocomial pneumonia occurring in a mechanically ventilated patient > 48 hours after intubation. It is categorized as early-onset (defined by most experts as 48-96 hours after intubation) and late-onset (> 2-96 hours after intubation): these differ with respect to responsible bacterial agents as well as outcomes. With an estimated incidence of 8-28% of intensive care unit (ICU) patients, or 13-35 cases per 1000 ventilator-days, VAP is common.[1,2]

The pathogenesis of VAP involves 2 key steps. The first is bacterial colonization of the aerodigestive tract due to disruption of normal host defenses. The second is aspiration of colonizing organisms from the aerodigestive tract into the lower respiratory tract[3]. Thus, anything that promotes bacterial colonization or aspiration may increase risk of VAP. There is a 1-3% increase in risk with each ventilator day. Nasal intubation, nasogastric tubes, re-intubation, frequent ventilator circuit changes, sedation and paralysis, and feeding patients in the supine position all amplify the risk. Specific patient populations appear to be more likely to develop VAP: patients undergoing cardiothoracic surgery or major abdominal surgery and those with head trauma, burn injuries or underlying COPD are some examples. Prior antibiotic use may offer some protection against early-onset VAP but seems to increase risk of late-onset VAP.[1-3]

How best to make the diagnosis of VAP remains controversial. Traditional clinical criteria (new or progressive radiographic infiltrates, leukocytosis, fever, new purulent sputum production) or the clinical pulmonary infection score are usually utilized with or without airway sampling.[1,4] Recent data demonstrate that addition of lower airway sampling significantly reduces inappropriate antibiotic use but does not impact overall survival.[5] Based on this, some experts recommend lower airway sampling as standard practice. Others suggest that diagnostic strategies without lower airway sampling may produce similar results if consistently combined with a protocol to limit antibiotic use.[6] Further studies are under way to try to resolve these issues.

The impact of VAP on patient outcomes is great. Attributable mortality is estimated to be 10-30% and is highest for late-onset VAP. In addition, VAP is associated with prolonged duration of mechanical ventilation and ICU and hospital stays as well as higher costs ($40,000 per patient).[1,2] VAP prevention programs have been shown to improve outcomes and reduce costs. Thus it is recommended that all ICUs have a defined VAP prevention program in place to monitor incidence and outcomes and update practice by implementing preventive strategies supported by clinical evidence and national guidelines.[3,7]

General Preventive Strategies

Hand-hygiene is one of the most essential and clearly effective methods of preventing nosocomial infections, including VAP. Use of alcohol-based (≥ 60%) disinfectants is the recommended method for hand-hygiene as it is more efficient and appears to improve compliance compared to usual hand-washing.[8] However, compliance remains unacceptably low at < 40-45% in most reports. Thus programs to monitor and improve adherence to hand-hygiene should be an essential part of every ICU.[9]

Increasing the use of non-invasive ventilation in appropriate circumstances (such as for acute respiratory failure in awake, alert COPD or CHF patients) will prevent VAP.[10] For patients who must be intubated, use of orotracheal (rather than nasotracheal) intubation and measures to avoid re-intubations will reduce VAP risk. The latter include minimizing unplanned extubation by securing endotracheal tubes and utilizing proper restraints and sedation levels, using non-invasive ventilation in appropriate circumstances and continuing to develop our understanding of how to predict successful extubation.[1,3]

Respiratory Care Issues

Multiple, controlled trials have demonstrated that frequent (daily or every 48 hours) ventilator changes do not reduce and may increase risk of VAP compared to less frequent (every 7-14 days or as needed).[11] Current recommendations are to change circuits only as needed. There is no clear data on the impact on VAP risk of the type of humidification system, in-line nebulizers vs metered-dose inhalers for bronchodilator delivery, closed vs open suction devices or routine chest physiotherapy.[7,12]

Patient Positioning

Studies using radioactively labeled gastric contents have demonstrated that reflux and aspiration of gastric contents are highest in the upine position and can be - reduced in a semi-recumbent position. Multiple epidemiological studies have identified supine body posi-

tion as a risk factor for VAP. Most recently, a randomized prospective trial of supine (0°) vs semi-recumbent (45°) position in 86 intubated, mechanically ventilated medical-respiratory ICU patients revealed a significant difference in VAP incidence (23% vs 5% for microbiologically confirmed pneumonia). The study was ended at the interim analysis due to this marked difference. The odds ratio of VAP for supine position was 6.8 (95% CI, 1.7-26.7). The effect was even greater for those patients receiving enteral nutrition in the supine position.[13] Further prospective studies of semi-recumbent positioning are under way. Although 1 small single-center trial should not usually change practice, I suggest considering this intervention in every ICU because it is a simple, safe and cost-free strategy that may make a big impact.

Feeding

Gastric feeding in the supine position and gastric overdistention are associated with a greater likelihood of reflux, aspiration and VAP. Thus feeding in a semi-recumbent position and careful advancement of feeds with monitoring of residuals and use of pro-motility agents as needed may normalize VAP risk.[3,13] Though it has been proposed that small-bowel feedings may reduce VAP risk, this has not been confirmed in randomized prospective trials.[14] Until such information is available, I suggest that gastric feeding in the semi-recumbent position be employed. Only when this cannot be instituted successfully should small-bowel feedings be considered.

Continuous Aspiration of Subglottic Secretions

Decreasing pooling of secretions (contaminated with bacteria) above the ETT cuff may reduce aspiration of these secretions into the lower airways and, in turn, prevent VAP. Specially designed ETTs allow continuous aspiration of subglottic secretions (CASS). Valles et al applied CASS in a randomized controlled trial in 190 medical-surgical ICU patients. They found a significant reduction in VAP (RR 1.98; 95% CI, 1.03-3.82 in control patients), particularly due to *H. influenza* and gram-positive organisms. The onset of VAP was also delayed by an average of about 6 days in patients receiving CASS.[15] Kollef et al randomized 343 cardiothoracic surgery patients to CASS or usual care. Though they observed less VAP in patients receiving CASS, this difference did not reach statistical significance. They did note, as Valles et al did, a delay in VAP onset as well as reduced Gram-positive and *H. influenza* infections in patients receiving CASS.[16] Thus CASS may reduce and/or delay onset of VAP. Because of the latter, CASS may have its greatest role in patients with anticipated short-term intubation. At this time, although CASS is not universally recommended, it should be strongly considered and evaluated by each ICU for incorporation into its VAP prevention program.[7]

Choice of Stress Gastritis Prophylaxis

Because gastric alkalinization is associated with gastric bacterial colonization, it has been postulated that stress gastritis prophylaxis with H2-blockers or proton-pump inhibitors may increase risk of VAP. Though smaller studies have shown a protective effect of sucralfate when compared to H2-blockers, a recent large multicenter clinical trial demonstrated no significant difference. Twelve hundred medical and surgical ICU patients requiring > 48 hours of intubation were randomized to receive either sucralfate or ranitidine. There was no significant difference in incidence of VAP (defined either clinically or with microbiological-confirmation) in either arm. There was also no difference in ICU length of stay or ICU mortality. There was, however, reduced GI bleeding with ranitidine (RR, 0.44; 95% CI, 0.21-0.92).[17] Thus, I suggest that mechanically ventilated ICU patients requiring stress gastritis prophylaxis should receive H2-blockers.

Selective Digestive Decontamination

Selective digestive decontamination (SDD) aims to limit or eliminate bacterial colonization of the oropharynx and GI tract of critically ill patients: a variety of regimens have been proposed including topical antimicrobials administered orally, intravenous (IV) antibiotics alone or a combination of topical and IV agents. The most commonly used topical pastes contain an aminoglycoside, polymyxin B and an antifungal agent. The usual IV antibiotic is a third-generation cephalosporin. Multiple clinical trials evaluating SDD over the past 2 decades were summarized in 2 recent meta-analyses which were critically appraised by Kollef in a recent commentary.[18] The key findings are: 1) the reduction in VAP and any mortality benefit reported with use of SDD are found principally in postoperative and trauma populations; 2) only the regimen combining topical and IV antimicrobials is effective; 3) there is considerable evidence of colonization with Gram-positive organisms, *Acinetobacter* and other resistant organisms in patients treated with SDD. Thus, SDD is not recommended for universal use. However, in select surgical ICUs and with close monitoring and surveillance for impact on institutional microbiology, SDD may be an important strategy for VAP prevention.

Table

Measures for Reducing the Incidence of Ventilator-Associated Pneumonia

Having a defined VAP surveillance and prevention strategy for every ICU;
Strict adherence to recommended hand-hygiene strategies and techniques;
Avoidance of intubation through the use of NPPV in selected patients, especially those with COPD exacerbations and congestive heart failure;
Use of orotracheal rather than nasotracheal intubation;
Avoidance of unplanned intubation through proper securing of endotracheal tubes, appropriate use of restraints, and effective sedation;
Changing ventilator circuits only when necessary;
Using semirecumbent positioning whenever possible, especially in patients receiving enteral feeding.

Kinetic Bed Therapy

There is some evidence to suggest the benefit of kinetic bed therapy in reducing VAP incidence in immobilized critically ill patients and stroke patients. The largest controlled study to date was done by Gentilello et al[19] in 60 ICU patients who were immobilized due to head injury or requirement for traction. They found a significant reduction in the combined end point of atelectasis and pneumonia with use of kinetic bed therapy but now for either alone. There are no larger studies and no controlled studies in other patient populations. No US or international critical care guidelines recommend this as a general measure: however, it is a part of the Canadian Critical Care Trials Group VAP Prevention guidelines.

Other

There is no defined role for IV prophylactic antibiotics or immune globulin for VAP prevention in the general critically ill population at this time.[3]

There is limited data on the efficacy of chlorhexidine oral rinse for reducing VAP risk in cardiothoracic surgery patients. Houston et al compared a 0.12% chlorhexidine rinse with Listerine in 561 patients undergoing cardiothoracic surgery. Though there was no difference in VAP overall, in retrospect, patients intubated for > 24 hours and with positive sputum cultures had significant reduction in VAP rates (58%).[20] Further study is warranted to confirm the benefit of chlorhexidine oral rinse and define appropriate patient populations for use. It is not recommended for use at this time.

In vitro and animal investigations demonstrate that silver-coated ETTs prevent *Pseudomonas* colonization.[21] Clinical utility is yet to be defined.

Conclusion

Available evidence supports the routine use of a number of specific measures to prevent VAP (*see Table*). Every ICU should have a VAP surveillance and prevention strategy in place. Careful monitoring and frequent updates are necessary for such a strategy to be effective. At a minimum, every ICU should encourage compliance with hand-hygiene. In addition, use of non-invasive ventilation when appropriate, orotracheal instead of nasotracheal intubation, orogastric instead of nasogastric tubes and change of ventilator circuits only as needed are all practices that should be in place universally. Semi-recumbent (45°) positioning should be strongly considered while further data are pending: it should at least be employed for all patients receiving gastric feedings. Finally, application of CASS and SDD should be individualized: in select ICU populations, these interventions are safe and important means of reducing VAP incidence. ■

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CME Questions

7. Which of the following is correct?
a. The most frequent manifestation of inhalational *B. cereus* infection is hemorrhagic mediastinitis.
b. The major toxins of *B. anthracis* are plasmid-encoded.
c. **B. anthracis** affects only severely immunocompromised individuals.
d. Isolation of *B. cereus* from vitreous culture of a patient with endophthalmitis after cataract surgery should be considered as insignificant.

8. Which of the following is correct with regard to the recommendations for blood cultures in adults made by Cockerill and colleagues?
a. Blood cultures should be incubated for 3 days, then discarded.
b. Only a single blood culture should be obtained within the first 24 hours.
c. When "paired" blood cultures are obtained, separate venipunctures are not indicated.
d. 20 mL should be obtained per venipuncture.

9. Which of the following is correct?
a. Antibiotic therapy does not affect sputum culture results.
b. Antibiotic therapy does not affect sputum Gram stain results.
c. Antibiotic therapy should be initiated within 8 hours of registration of a patient with community-acquired pneumonia.
d. The sensitivities of Gram stain and culture, when sputum was obtained prior to antibiotic administration, were 80% and 93%, respectively.

Answers: 7. (b); 8. (d); 9. (d)

Correction

The August 2004 *Infectious Disease Alert* from "Find the VRSA in the MRSA: Get an Etest!" article: 1st and 2nd paragraphs, measurements should be µ/mL instead of mg/mL. ■

In Future Issues:

A New Treatment for Giardiasis

UPDATES

By Carol A. Kemper, MD, FACP

Bed Bugs Are Back

ProMED-mail Post, April 15, 2004; www.promedmail.org

Since the mid-1990s, public health officials have been noticing a steady resurgence in the United States, the United Kingdom, and in Europe of an age-old pest—bed bugs, all countries where bed bugs had been more or less non-existent for the past 20-30 years. Bed bugs, which are fairly ubiquitous in developing countries, enjoy cozy warm surroundings, such as the seams of your mattress. They can survive for up to 1 year without feeding, which means they can survive even in stored furniture. The reason for their resurgence in the United States and the United Kingdom is not clear, but with the increase in international travel to developing countries, the bugs may simply be hitching a ride home in your luggage. It is also suspected that broad resistance to insecticides may be occurring, especially to permethrin, which is widely used in mosquito netting.

The predominate species, *Cimex lectularis*, and its tropical cousin, *Cimex hemipterus*, are night feeders, and actively suck blood from small vessels in the skin. Mature adults measure about 5 mm in length and are readily visible to the naked eye—if you know where to look for them. They require ~10-20 minutes to become fully engorged, and multiple bites are common. Although, for the most part, they are considered more pests than potential vectors of disease, the bites can cause erythema and itching, sleeplessness, and even anemia, especially in babies or small children. While there is some evidence that hepatitis B surface antigen may be present for up to 6 weeks in a bed bug (and HIV can survive in the mouthparts for 1 hour), there is thus far, no good evidence that bed bugs play a role in the transmission of these organisms. ■

Can You Guess the Pathogen?

I recently saw a 38-year old, otherwise healthy woman, referred to my office with a 2.5 cm necrotic anterior shin wound. The problem started about 3 months earlier, when she noticed a small non-tender papule, initially thought to be a small focus of folliculitis from shaving. She was a frequent flier at her local nail salon, where she received a pedicure every 3 weeks, using one of those new-fangled spa chairs with the whirlpool foot bath. The lesion gradually enlarged, began draining serous fluid, and eventually ulcerated. She failed to respond to several attempts at debridement and treatment with cephalexin. An initial biopsy revealed only chronic inflammation, and routine cultures were unremarkable. About 2 months after the initial papule had appeared, she developed a second, smaller (~0.5 cm) satellite lesion, just medial to the primary lesion. A repeat biopsy, again, showed chronic inflammation, and cultures grew. . . .*Continued on next page*.

If It Was a Bear, It Would Have . . .

Kunimoto D, et al. *J Clin Micro.* 2004; 42:3374-3376.

I remember as a kid, standing in awe, in front of a nearby lake home in northern Minnesota, from which the siding had been literally ripped off, right down to the plywood, by a hungry bear trying to get at the garbage left inside. The claw marks left on the fragments of siding left a strong impression. Fortunately, brown bears seldom attack people (or, you hope they read the same book about bears as we do), but they will rip the door off your car trying to get to the make-up bag or cooler left inside.

Grizzlies are another thing—for example, in Alberta, Canada, 69% of serious and fatal bear attacks are by grizzlies, although they make up only 2.5% of the bear population. The unfortunate hunter in this report was out hunting elk east of Banff National Park when he was attacked by a grizzly bear. He sustained deep wounds to his scalp and shoulders, with teeth marks evident on the cranium. The wounds were debrided, and intraoperative cultures grew a variety of aerobic Gram-positive and Gram-negative organisms, including *Serratia fonticola*, *Serratia marcescens*, *Aeromonas hydrophila*, *Bacillus cereus*, and *Enterococcus durans*. The Gram-negative organisms were resistant to ampicillin, cephazolin, and cefuroxime. Interestingly, no anaerobes were isolated. He responded well to 1 week of piperacillin-tazobactam, followed by 3 weeks of ciprofloxacin.

Other investigators have also noted a lack of anaerobes in cultures taken from bear mouths and bear wounds. Most surveys, of which there are few, have demonstrated *Staphycoccus areus*, *S. epidermidis*, and Gram-negatives. Whether this is due to the difficulty in isolating anaerobes, possibly in more remote locations, is unknown. But it is interesting to speculate that

diet may play a role. While bears are omnivores, 90% of their diet is derived from vegetable matter, berries and roots, punctuated by the occasional squirrel, beetle, or deer. In contrast, anaerobes appear to be more common in more preditory meat-eaters, such as humans, felines, and dogs—where anaerobes may play an important role in the pathogenicity of bite wounds. ■

. . .*Continued from previous page*

Mycobacterium chelonae vs *abscessus*. She was initially treated with clarithromycin, doxycycline, and ethambutol pending identification of the organism, followed by a combination of clarithromycin and doxycycline, with a good response, but modest residual scarring.

Skin and soft tissue infections due to the atypical mycobacteria *M. fortuitum*, *M. chelonae*, and *M. abscessus* are popping up with increasing frequency in nail salons, beauty parlors, and following cosmetic surgery. These rapid growers are ubiquitous in soil and water. Winthrop and colleagues documented the first large-scale outbreak of *M. fortuitum* furunculosis in ~115 persons from a single nail salon, which used a whirlpool foot bath.[1,2] Since then, nail salon whirlpool foot baths are being increasingly recognized as a cause of both sporadic and community outbreaks of atypical mycobacterial skin and soft tissue infections. Most of the reported cases of salon-related infection have been due to *M. fortuitum*, although any of the atypical mycobacterium, including *M. avium*, can happily survive in warm spa water and cause localized skin infection. In the larger outbreak above[1], lesions due to *M. fortuitum* typically first presented as a small papule, with progression to large fluctuant boils, with frequent ulceration. Multiple lesions were common, but only 1 apparently healthy individual developed lymphatic spread. Histopathology variously showed chronic inflammation and necrosis, with more acute lesions occasionally showing granulomata. AFB were visualized in only 1 of 15 specimens (7%). Most of the *M. fortuitum* isolates were susceptible to amikacin (100%), ciprofloxacin (100%), minocycline (100%), cefoxitin (91%), doxycycline (89%), and septra (61%); only a minority were sensitive to the macrolides. Patients received a mean duration of 4 months of therapy, and scarring was common.

Although *M. chelonae* has also been implicated in whirlpool bath infections, it has more frequently been associated with skin and soft tissue infection due to cosmetic procedures.[3-5] In New York City, in 2002, 25 cases of infection due to *M. chelonae* occurred in persons receiving various cosmetic injections, such as silicone and collagen.[4] Following this outbreak, officials cracked-down on unlicensed cosmetologists in NYC. Most recently, 12 cases of *M. chelonae* infection were reported following various plastics procedures (including breast implants, breast lifts, and tummy tucks) in the Dominican Republic.[5]

The diagnosis of these infections can easily be delayed or missed unless the clinical suspicion is high. While the rapid growers can grow on routine media if held long enough, they are often missed in routine cultures. Swab cultures are also low yield, and AFB smears are seldom positive. Thus, tissue biopsy with mycobacterial culture is key to the diagnosis of these infections. ■

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More Bites . . .

ProMED-mail post, July 15, 2004; www.promedmail.org.

FELINE IMMUNODEFICIENCY VIRUS is spreading rapidly through the lion population in Kruger National Park in South Africa. The *Harare Herald* recently reported in mid-July that up to 60-80% of the lions in the southern portion of the park are now infected with the AIDS-like virus, although lions in adjoining areas in Zimbabwe and Mozambique thus far show no evidence of disease. Nonetheless there is considerable concern that infection will quickly spread to other parts of the park, as male lions have quite a wide migratory range. Lions are especially vulnerable because of their social structure in prides, with close physical contact, in contrast to cheetahs and leopards, which are more solitary. The disease is very similar to HIV: It is spread through bites and sexual contact. Affected animals eventually succumb to wasting, neurologic disease and infection. ■

PHARMACOLOGY WATCH

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.*

New Clinical Guidelines on Cholesterol Management

The National Cholesterol Education Program (NCEP), a product of a collaboration of the National Heart, Lung, and Blood Institutes, the American College of Cardiology, and the American Heart Association, has updated its clinical practice guideline on cholesterol management. Based on several recent studies, that suggest that aggressive lowering of LDL cholesterol benefits high-risk patients, the new guidelines recommend aggressive treatment for patients who are at risk for coronary artery disease. Specifically, patients who are defined as "very high-risk" should be considered for aggressive treatment. Very high-risk patients are defined as those who have cardiovascular disease together with multiple risk factors (especially diabetes), severe and poorly controlled risk factors (such as continued smoking), or metabolic syndrome. The guideline had previously recommended drug therapy in these patients only if the LDL cholesterol was greater than 130 mg/dL, with a goal of 100 mg/dL. The new guideline recommends a treatment threshold of 100 mg/dL, with a goal of 70 mg/dL. "High-risk patients" are defined as those who have coronary heart disease, cerebrovascular disease, peripheral vascular disease, diabetes, or 2 or more risk factors (such as smoking or hypertension) that give a greater than 20% chance of having heart attack within 10 years. The LDL goal for these patients remains 100 mg/dL or less, and the new guideline now recommends drug treatment for those high-risk patients with an LDL > 100 mg/dL. Moderately high-risk patients are defined as those with 2 or more risk factors for coronary heart disease and a 10-20% risk of heart attack within 10 years. For these patients, drug therapy is recommended to lower LDL cholesterol under 130 mg/dL, and the option is given to treat to levels under 100 kg/dL. For lower-risk patients, the guideline was not changed. Drug therapies recommended by the NCEP include statins, bile acid resins, nicotinic acid, and ezetimibe. As in previous NCEP guidelines, the role of lifestyle modification is stressed. The full guideline can be viewed in the July 13th issue of *Circulation*, and highlights can be reviewed on-line at www.nhlbi.nih.gov.

Hypothyroidism and Pregnancy

A new study clarifies thyroid replacement therapy during pregnancy. Researchers at Harvard followed 19 women with hypothyroidism through 20 pregnancies, of which 17 resulted in full-term births. Thyroid function, HCG levels, and estradiol were measured before conception, every 2 weeks for the first trimester, and monthly thereafter. Oral doses of levothyroxine were increased during pregnancy to maintain preconception levels. The mean levothyroxine requirements increased 47% during the first half of pregnancy, plateaued by week 16, and remained

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stable until delivery. The authors recommend that hypothyroid women, who become pregnant, should increase their levothyroxine dose by 30% as soon as pregnancy is confirmed, and should be monitored carefully throughout the duration of their pregnancy (*N Engl J Med*. 2004;351:241-249). Although simple in its design, this is an important study because it is estimated that 1 to 2% of all pregnant women are hypothyroid and need replacement therapy. Hypothyroidism during pregnancy is associated with poor fetal outcomes including impaired cognitive development and increased mortality. Clinicians now have a clear guide to levothyroxine dosing changes during pregnancy.

Anti-Depressants and the Risk of Suicide

The risk of suicidal behavior is relatively high after starting anti-depressants, however, there is no statistical difference between anti-depressants used, according to a new study. Researchers reviewed data from the UK General Practice Research Database from 1993 to 1999, and compared nearly 160,000 users of 4 anti-depressant drugs, 2 SSRIs and 2 tricyclics; fluoxetine, paroxetine, amitriptyline, and dothiepin (a trycyclic anti-depressant not marketed this country). The outcome was first-time non-fatal suicidal behavior, or suicide in treated patients vs comparable patients who did not exhibit suicidal behavior. The relative risks for non-fatal suicidal behavior were 0.83 for amitriptyline (95% CI, 0.61-1.13), 1.16 for fluoxetine (95% CI, 0.90-1.50), and 1.29 for paroxetine (95% CI, 0.97-1.70), compared to those using dothiepin. Perhaps the most startling finding in this study was the 4.07 relative risk for suicidal behavior within 9 days of starting any anti-depressant (95% CI, 2.89-5.74), compared to patients prescribed an anti-depressant 90 days or more before their suicidal behavior. Even more concerning, was a relative risk for fatal suicide among new users of anti-depressants of 38.0 (95% CI, 6.2-231). The authors found no significant associations between use of the various anti-depressants and the risk of suicide (*JAMA.* 2004;292:338-343, ed 379-380). The accompanying editorial points out the timeliness of the study, with regard to current congressional hearings in the use of anti-depressants in young adults. The authors point out that the data on patients aged 10 through 19 is limited however, and further study may be needed in this group.

FDA Actions

The FDA has approved acamprosate (Campral-Merck) for the maintenance of abstinence in patients in alcohol recovery programs. The drug, which has been available in Europe for several years, may not work if patients are still drinking or abusing other drugs when initiating therapy. Acamprosate's mechanism of action is unknown, but it appears to act in the central nervous system. Common side effects include diarrhea, nausea, vomiting, and abdominal pain.

The FDA has approved Merck and Schering-Plough's Vytorin for the treatment of hypercholesterolemia. The drug combines Merck's simvastatin (Zocor) with the jointly developed ezetimibe (Zetia), and is touted to be as potent as the so-called "super statins" atorvastatin (Lipitor) and rosuvastatin (Crestor). The new drug, which is expected to garner a hefty market share, will be priced at $2.30 a pill and should be available this fall.

Imiquimod (Aldera-3M) has received the expanded indication for treatment of superficial basal cell carcinoma. The drug, which is a topical immune modulator, was recently approved for treatment of actinic keratosis, and was initially approved for the treatment of venereal warts.

Brief Notes

The over-the-counter cough medications, dextromethorphan and diphenhydramine, are no better than placebo in suppressing cough in children (*Pediatrics.* 2004;114:e85-e90).

Many women are turning to phytoestrogens in lieu of hormone replacement therapy. The most commonly used of these, isoflavone soy protein, does not improve cognitive function, bone mineral density, or plasma lipids in healthy postmenopausal women (*JAMA.* 2004;292:65-74).

Ginseng reduces the effectiveness of warfarin in healthy volunteers. Patients on warfarin should be questioned as to their herbal supplement use (*Ann Intern Med.* 2004;141:23-27).