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## INSIDE



# Adjunct Dexamethasone Therapy for Hematogenous Suppurative Arthritis

ABSTRACT & COMMENTARY

***Synopsis:*** *Short-course (4 days) adjunct dexamethasone therapy for hematogenous suppurative arthritis in children shortened the duration of symptoms during the acute phase and reduced residual dysfunction at the end of therapy, and at 6 and 12 months.*

**Source:** Odio CM, et al. Double blind, randomized, placebo-controlled study of dexamethasone therapy for hematogenous septic arthritis in children. *Pediatr Infect Dis J*. 2003;22:883-888.

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL OF short-course dexamethasone therapy as an adjunct to antimicrobial therapy was conducted among children 3 months to 11 years of age with hematogenous suppurative arthritis in Costa Rica from 1998 to 2000. After enrollment, children were randomized 1:1 to receive dexamethasone 0.2 mg/kg/dose intravenously every 8 hours for 12 doses (4 days), or saline of the same volume and regimen. Of 123 children who were enrolled, 50 patients in the control group and 50 patients in the treatment group were evaluable. A pathogen was isolated from all evaluable subjects: *Staphylococcus aureus* accounted for 67% of isolates, *Haemophilus influenzae* type b for 13%, and *Streptococcus pneumoniae* for 9%. All *H influenzae* type b were susceptible to ampicillin, and all *S pneumoniae* were susceptible to penicillin. (The study was initiated 2 months before the conjugate *H influenzae* type b vaccine was available for all of Costa Rica.)

Dexamethasone and placebo patients had a normal CRP at 2.04 ± 1.25 days and 4.68 ± 6.23 days of therapy, respectively ($P = .01$), and resolution of fever, pain, and limitation of range of motion of the joint at 2.3 ± 6.1 days and 7.8 ± 2.0 days, respectively ($P = .001$). The duration of intravenous/oral antibiotics was 7.2 ± 1.2/7.2 ± 2.5 days for dexamethasone patients, and 10 ± 5.6/9 ± 2.6 days for placebo patients. The number of arthrocenteses and arthrotomies was similar. Bone involvement documented by bone scan was documented in 6 dexamethasone and 6 placebo patients.

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At the end of antimicrobial treatment, 2 dexamethasone patients had residual dysfunction, compared to 16 placebo patients with dysfunction ($P < .001$). At 12 months, 1 dexamethasone patient had residual hip dysfunction with impaired angles of movement, limping, and shortening (2 cm) of the affected extremity. In contrast, 13 placebo patients ($P < .001$) had residual joint dysfunction—12 patients with hip involvement with impaired angles of movement including 6 with limping and 5 with shortening of the affected extremity, and 1 patient with impaired angles of movement, limping, and pain.

### COMMENT BY HAL B. JENSON, MD, FAAP

A short course of dexamethasone, combined with traditional antibiotic treatment, significantly shortened the duration of inflammatory symptoms associated with microbiologically confirmed hematogenous suppurative arthritis and reduced residual joint dysfunction in children at the end of treatment, at 6 months, and at 12 months. The incidence of residual dysfunction in the placebo patients was 26%, similar to the incidence of 23% that has been previously reported.

The short-term benefits of dexamethasone in reducing signs of inflammation, especially fever, and in facilitating symptomatic improvement is not unexpected. More importantly, the long-term (at least at 12 months) benefit of adjunct dexamethasone in reducing residual joint dysfunction is an important new finding. This study suggests a benefit of early anti-inflammatory treatment to mitigate the additional damaging effects of inflammation, reducing inflammation until the bactericidal effect of the antibiotic therapy becomes established. The actual mechanism of this effect, if confirmed, remains to be elucidated.

This was a small study of 100 patients among children all younger than 12 years of age. The benefits suggested by this study need to be replicated among a larger group of children and also among adults. Additional studies of hematogenous suppurative arthritis should include measurements of cytokines in serum and synovial fluid as a marker of the inflammatory response. Nevertheless, this study poses an interesting finding that may have an effect, if confirmed in larger trials, on the routine management of hematogenous suppurative arthritis in children. ■


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# Treatment of Ventilator-Associated Pneumonia: Longer Is Not Better

ABSTRACT & COMMENTARY

***Synopsis:*** *Antibiotic administration for only 8 days to patients with ventilator-associated pneumonia was not inferior to 15 days of therapy.*

**Source:** Chastre J, et al. Comparison of 8 vs 15 days of antibiotic therapy for ventilator-associated pneumonia in adults. *JAMA*. 2003;290:2588-2598.

CHASTRE AND COLLEAGUES PERFORMED A RANDOMized, double-blind trial in 51 French ICUs to compare the efficacy of treatment of ventilator-associated pneumonia (VAP) for a duration of either 8 or 15 days. Patients receiving mechanical ventilation for a minimum of 48 hours were eligible if they had clinical evidence of VAP, significantly positive quantitative cultures of distal pulmonary secretions (BAL or protected brush or catheter), and received appropriate empirical antimicro-

bial therapy within 24 hours following bronchoscopy. Patients whose pneumonia developed within the first 5 days of mechanical ventilation and who had received no antimicrobial therapy in the 15 days preceding infection were excluded, as were those who were significantly immunocompromised and/or had a SAPS score > 65. Patients were randomized after bronchoscopy to receive antibiotic therapy selected by the clinician for either 8 or 15 days; blinding was maintained until day 8. The sample size selected was designed to demonstrate noninferiority (upper limit of confidence interval < 10% of the difference in outcomes) of the 8-day regimen with regard to mortality and pneumonia recurrence and superiority with regard to total antibiotic use.

A total of 401 patients were enrolled; the 2 treatment groups were similar except that there were significantly more females in the 15-day treatment group. Approximately one-fifth of the pathogens isolated in significant numbers in each group were *P aeruginosa,* and 7% were MRSA.

Patients assigned 8 days of therapy had, as expected, more antibiotic-free days (13.1 vs 8.7; $P < .001$) than those randomized to receive antibiotics for 15 days, but there was no significant difference between the 2 treatment groups with regard to 28-day mortality (18.8% vs 17.2%) or recurrent infections (28.9% vs 26.0%). There was also no significant difference with regard to number of days free of mechanical ventilation or days free of organ failure, nor in length of ICU stay. Recurrence of pulmonary infection, however, occurred more frequently in the 8-day than the 15-day group (40.6% vs 25.4%; 90% CI for the difference, 3.9-26.6%) among those whose primary infection was caused by a nonfermenting Gram-negative bacillus.

## COMMENT BY STAN DERESINSKI, MD, FACP

"Are minimization of selection of resistant organisms and maximization of individual outcome mutually exclusive?"[1] This title of a recent publication establishes the dilemma faced by the clinician in his or her decisions regarding antibiotic therapy. Maintaining this delicate but crucial balance is of prime importance.

While VAP is an infection associated with great morbidity and high mortality, its diagnosis and treatment are fraught with uncertainties. Only approximately one-third of pulmonary infiltrates in surgical ICU patients are due to infection.[2] Qualitative cultures of respiratory secretions may be misleading. The initial empiric choice of antibiotic is critical to a favorable outcome. Finally, once antibiotic therapy has been initiated, there has been limited guidance available to the clinician to provide a rational for its discontinuation. There are, in fact, very few infectious diseases for which we know the optimal duration of antibiotic therapy. This is not a trivial issue because unnecessary continuation of antibiotic administration beyond the point of maximal efficacy only contributes to an increased risk of drug-related adverse effects and to an increase in prevalence of antibiotic-resistant organisms. The latter is an especially recalcitrant problem in many ICUs. A recent international conference came to a consensus regarding the management of VAP: "No consensus was reached regarding choices of antimicrobial agents or the optimal duration of therapy."[3]

The most recent American Thoracic Society consensus statement, published in 1996, recommends that nosocomial pneumonia be treated with antibiotics for 14-21 days.[4] This recommendation was not, however, evidence based. Nonetheless, this seems to be the usual answer given to the question concerning the duration of antibiotic therapy for this infection although, in practice, it is not uncommon for antibiotics to be continued for the duration of a patient's stay in the ICU. It is difficult to argue against the observation that antibiotics are vastly overused in that setting.

Chastre et al acknowledge some of the shortcomings of their investigation, at least 2 of which may be of some importance. Almost two-thirds of the 1171 patients assessed where excluded. Thus, the patients studied represented a highly selected group of all patients. Second-

**Table**

### Suggested General Approach

1. Make a clinical diagnosis of VAP. Calculate CPIS.
2. Obtain blood cultures and quantitative cultures of respiratory secretions. Specimens obtained by blind endotracheal aspiration are acceptable.
3. Start broad-spectrum antibiotic therapy, keeping in mind the local susceptibility patterns, the presence of local pathogens (eg, *Legionella* spp.), and any antibiotic the patient may have recently received. Do not start vancomycin or linezolid in the absence of Gram-positive organisms seen on Gram stain of respiratory secretions.
4. At approximately 72 hours, clinically re-evaluate the patient, recalculate the PORT score, and evaluate the microbiological data.
   a. If the CPIS score is ≤ 6 and this low likelihood of VAP is confirmed by good clinical judgment, and if the quantitative microbiologic data fail to meet the appropriate threshold (BAL: > $10^4$ cfu/mL; protected brush: > $10^3$ cfu/mL; ETA: > 105 cfu/mL), discontinue antibiotic therapy.
   b. If antibiotic therapy continues to be indicated, adjust therapy to reflect the culture and susceptibility results. When possible, de-escalate therapy to a narrower spectrum.
5. On day 8, discontinue antibiotic therapy if the patient has improved. In the absense of improvement, re-evaluate therapy.

ly, the study was not blinded beyond 8 days, opening the door to potential investigator bias. Despite these issues, Chastre et al have made a significant contribution to attempts to rationalize the management of VAP.

Another caveat in the application of these results in the clinic is the finding of a greater rate of recurrence (mostly apparent relapses—no genetic analyses of isolates was performed) among the patients whose primary infection was due to nonfermenting aerobic Gram-negative bacilli, primarily *P aeruginosa*. This is not terribly surprising, given the difficulty in eradicating this organism. Nonetheless, this result was not reflected in overall outcomes, indicating that these recurrences are manageable.

This study and others allow a listing of some of the principles that have emerged that allow for better management of VAP, including the following:

1. Early institution of appropriate antibiotic therapy (ie, antibiotics that prove to be active against the bacteria causing the pneumonia) is critical to a successful outcome.[5]
2. The Clinical Pulmonary Infection Score (CPIS) is reasonably useful in the diagnosis of VAP, especially when combined with microbiological data, in the diagnosis of VAP.[6]
3. The Gram stain is of value, particularly in excluding the presence of significant numbers of Gram-positive organisms.[7]
4. Quantitative cultures of respiratory secretions provide useful information in the diagnosis of VAP that may affect outcome.[8] While some prefer specimens obtained by BAL, mini-BAL, or protective brush catheter, endotracheal aspirate cultures demonstrate excellent correlation with quantitative cultures obtained by these more technical and expensive methods.[9,10]
5. The absence of clinical or microbiological data confirmatory of the presence of VAP after 48-72 hours in a patient with a low probability of pneumonia at baseline is an indication to discontinue empiric antibiotic therapy instituted for treatment of presumed pneumonia.[11]
6. De-escalation of antibiotic therapy (ie, narrowing of the antibacterial spectrum in response to culture and susceptibility data) is indicated when possible.[12] "Double coverage" may be warranted in some circumstances (eg, *P aeruginosa* infections).
7. In most cases, no more than 8 days of antibiotic therapy are required.

These principles can be used in the development of guidelines for the management of VAP. One example, the detailed guidelines in use at the University of Virginia, is available on the Internet.[13] ■

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# Do Isolation Precautions for MRSA Compromise Patient Care?

ABSTRACT & COMMENTARY

***Synopsis:*** *As determined by process of care measurement, adverse event occurrence, and patient satisfaction, quality of care is compromised by infection control procedures.*

**Source:** Stelfox HT, et al. Safety of patients isolated for infection control. *JAMA*. 2003;290:1899-1905.

To determine whether isolation procedures used for control of methicillin-resistant *Staphylococcus aureus* (MRSA) in hospitals might affect patient safety, Stelfox and associates retrospectively reviewed data from 2 large, urban teaching hospitals: Sunnybrook and Women's College Health Sciences Centre in Toronto and Brigham and Women's Hospital in Boston.

Stelfox et al analyzed 2 sets of patients: a consecutive series of adults admitted to the Toronto hospital for a 1-year period and a series of adult patients consecutively admitted to the Boston hospital during a 3.5-year period with a diagnosis of congestive heart failure (CHF). The latter group was studied because established standards of care relating to management of CHF facilitated an objective measurement of quality of care. In each series, patients who were managed with contact precautions, as specified by Centers for Diseases Control and Prevention guidelines, were matched to controls (2 control patients for each isolated patient) by identifying patients who occupied each isolated patient's hospital bed immediately before and immediately after the isolated patient. Isolated patients were either colonized (in 96% of cases) or infected (in 4%) with MRSA.

Safety was assessed by 3 criteria: process of care, adverse events, and patient satisfaction. Process of care was a surrogate for thoroughness of care and included indicators such as vital sign recording, presence or absence of nurses' and physicians' notes, and in the CHF cohort, whether left ventricular function and ejection fraction were evaluated, whether education efforts were documented, and if follow-up appointments were scheduled. Adverse events served as a marker for outcomes of care and included injuries that lengthened hospital stay, produced disability, or resulted in abnormal laboratory test results. Patient satisfaction was assessed by identifying instances of patients' leaving against medical advice, complaints about medical care, and altercations or suicide attempts.

The results? Isolated patients received a lower level of care, as reflected in vital sign deficiencies, absence of nurses' and physicians' notes, documentation of patient education and follow-up appointment scheduling, and differences in medications prescribed upon hospital discharge. In addition, isolated patients had an increased incidence of such adverse events as falls, pressure ulcers, and fluid and electrolyte disorders. Patient satisfaction was much lower in isolated patients than in controls (isolated patients were 23 times more likely to have lodged a complaint).

No differences in hospital mortality were observed.

## COMMENT BY JERRY D. SMILACK, MD

This sobering, provocative report raises important questions that are infrequently asked whenever isolation procedures are instituted. In our quest to limit transmission of infections to patients and to ourselves, do we inadvertently reduce the level of care to isolated patients? What is the psychological effect of isolation on patients and their visitors?

Others[1,2] have noted that health care worker contact with patients is reduced when isolation precautions are imposed. In the present study, Stelfox et al have carefully documented serious safety and medical care deficiencies associated with isolation precautions for MRSA. Since data were gathered primarily by retrospective chart review—with its attendant reliance on documentation—one might wonder what additional deficiencies would have been observed had concurrent review been in place.

Stelfox et al correctly call for further studies to determine whether certain components of isolation procedures might be more important for control of infection but less deleterious than others. They also wonder whether their findings apply to hospitals of smaller sizes or different locales. ■

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# A Comeback for Colistin?

ABSTRACT & COMMENTARY

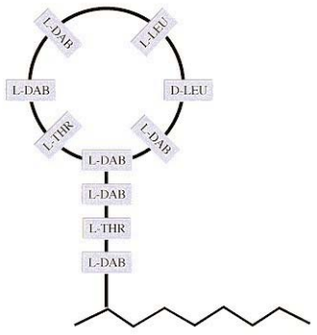
***Synopsis:*** *The 50-year-old drug colistin was used successfully in 14 of 23 cases of serious infections caused by multiply resistant* Pseudomonas aeruginosa.

**Source:** Linden PK, et al. Use of parenteral colistin for the treatment of serious infection due to antimicrobial-resistant *Pseudomonas aeruginosa*. *Clin Infect Dis*. 2003;37:e154-e160.

COLISTIN WAS USED AS SALVAGE THERAPY FOR 23 critically ill patients with serious hospital-acquired pneumonia caused by *Pseudomonas aeruginosa* uniformly resistant to the β-lactams piperacillin, ceftazidime, cefepime, aztreonam, imipenem, the aminoglycosides gentamicin and tobramycin, as well as the fluoroquinolone ciprofloxacin. All patients had been admitted to an abdominal organ transplantation unit at the University of Pittsburgh Medical Center between January 1996 and February 2003. All patients were in intensive care, and all had evidence of pneumonia as defined by the American Thoracic Society.[1] Twenty-two of the patients were receiving mechanical ventilation, and 21 were being given artificial kidney support at the start of therapy. Infections at additional sites affected 5 patients. Colistin was administered intravenously via catheter at a dose of 2.5 mg/kg q.12h. when serum creatinine was < 2.5 mg/dL, the same dose once daily when the serum creatinine was between 2.6 and 4 mg/L, or as a single 1 mg/kg dose per day when the serum creatinine was > 4 mg/dL for a median of 17 days (range, 7-36 days). The drug was given as monotherapy in 10 cases or combined with amikacin in 4 cases or a ß-lactam in the remaining cases. A favorable clinical response was observed for 14 patients (61%); 3 patients experienced relapse, and 7 patients died during therapy. Bacteremia affected 8 patients and was the only significant factor associated with treatment failure ($P$ = .02). Colistin proved safe and was well tolerated by all except one patient who developed diffuse weakness that resolved after temporarily stopping therapy. Colistin affords salvage therapy for those patients with infections due to *P aeruginosa* that might otherwise have prove untreatable.

**Figure 1.**

**A Schematic Representation of Colistin**




L-DAB = L 2,4-diaminobutyric acid; L-THR = L-threonine; L-LEU = L-leucine; D-LEU = D-leucine

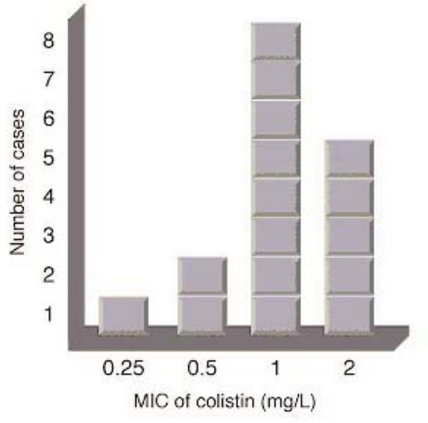
## COMMENT BY J. PETER DONNELLY, PhD

Colistin is a basic cyclic polypeptide (*see Figure 1*) also known as polymyxin E and is a relative of polymyxin B. The drug originates from the Gram-positive spore-forming rod of *Bacillus polymyxa var. colistinus*. It is not surprising that all Gram-positive bacteria such as *Staphylococcus aureus* are resistant. Some Gram-negative bacteria including *Proteus* species and *Burkholderia cepacia* are also inherently resistant. Hence, colistin is a narrow-spectrum drug active against enteric Gram-negative bacilli such as *Escherichia coli* and, of course, *P aeruginosa*.

Despite celebrating 50 years of use, its exact mode of action remains incompletely known, but it appears to disrupt cell membrane function. This may be because its use was superseded by the introduction of the anti-pseudomonal aminoglycosides and penicillins and later the cephalosporins, carbapenems, and fluoroquinolones. The MICs of colistin for *P aeruginosa* lie close together between 0.25 and 2 mg/L (*see Figure 2*) and are no different today than they were 50 years ago. So, despite *P aeruginosa* being very adept at developing resistance to a whole range of antimicrobial agents, the polymyxins

**Figure 2.**

**MICs of Colistin for *Pseudomonas aeruginosa***



seem to remain a notable exception. Others have also resorted to colistin for similar reasons[1-7] prompting the headline "Colistin: An antimicrobial for the 21st century?"[8] The answer seems to be affirmative for settings similar to those described here.

The pharmacokinetics of the drug are poorly defined.[9] A variety of adverse drug reactions have been ascribed to colistin, including neurotoxicity (apnea, perioral and peripheral paraesthesia, vertigo; rarely vasomotor instability, slurred speech, confusion, psychosis, visual disturbances) and nephrotoxicity. Hypersensitivity reactions have also been reported (www.x-gen.us/ProductInserts/Colistimethate_info.pdf). However, the development of such reactions is thought to be due to not following the manufacturer's instructions carefully enough. Moreover, the fact remains that experience with this drug is limited because its use was largely abandoned once safer and better alternatives were available. Linden and colleagues use phrases like "resurrection" and "agent of last resort" to underscore the desperation encountered when faced with a "dangerous therapeutic void," as in their case. The drying up of the pipeline for new drug products to tackle multiple resistance only adds to this sense of doom. Whether they are right in their assessment, the dearth of new antibacterial agents looks set to continue. The message also seems clear. We are just going to have to make the best of what we have in our antimicrobial armamentarium. With drugs like colistin, we may even have to learn not only when, but also how, to use them safely and most effectively. ■

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# ICAAC/IDSA/ASTMH 2003

CONFERENCE COVERAGE

*The following summary of selected abstracts from 3 meetings will be published in multiple parts. The 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) met in Chicago September 14-17, 2003. The Infectious Disease Society of America (IDSA) met in San Diego October 9-12, 2003. The American Society of Tropical Medicine and Hygiene met in Philadelphia December 3-7, 2003. —* ***Stan Deresinski, MD, FACP***

## Gram-Negative Bacilli

### Antibiotic Therapy

Monte Carlo simulations were performed to determine pharmacodynamic parameters in critically ill patients based on published pharmacokinetic data. For organisms at the NCCLS breakpoint, the probability of achieving an optimal pharmacodynamic parameter with standard dosing of either imipenem or cefepime was 64%, while it was 55% for ceftazidime and 14% for ciprofloxacin. With piperacillin/tazobactam, it was 70% for *Enterobacteriaceae* and 39% for other Gram negatives (*IDSA 194*).

The initial choice of antibiotic therapy is critical to a successful outcome in patients with life-threatening infections. A retrospective review of 133 episodes of multidrug-resistant Gram-negative bacteremia in ICU patients undergoing regular multisite surveillance cultures found that 80% of those bacteremias were preceded by detectable colonization. Of those with colonization, initial empiric antibiotic therapy was appropriate in 77%, while in those without prior detectable colonization, it was appropriate in only 56% ($P = .037$) (*ICAAC K-699*).

A meta-analysis of 17 studies of Gram-negative bacteremia (only 1 of which was a prospective, randomized

trial) failed to find evidence of reduced mortality in patients given combination therapy as opposed to monotherapy (*ICAAC K-700*).

Polymyxin B, given intravenously for a mean duration of 15.8 days, produced a 54% microbiological and 96% clinical cure rate in 26 patients with multidrug-resistant Gram-negative infection. No nephrotoxicity was seen, but 1 patient had lower extremity weakness attributed to the drug. Eight patients with nosocomial infection caused by multidrug-resistant *A baumannii* and *P aeruginosa*, 5 of whom were bacteremic, were treated with intravenous colistin. Seven survived and did not develop renal toxicity. The death was due to sepsis on day 4 of therapy. Finally, polymyxin B was administered to 20 patients with resistant Gram-negative infections by intravenous (76%), intraventricular (10%), and inhalational (14%) routes. Infection was cleared in 80%. One patient had a doubling of serum creatinine, 1 had rash, and 1 had muscle weakness (*ICAAC K-701s, K-712, K-702*).

**ESBL-Producing Organisms**

Extended spectrum β-lactamases (ESBL) continue to expand in number and type, in bacterial host range, and in geographic extent. The prevalence of fecal carriage of ESBL-producing *Enterobacteriaceae* among outpatients in Madrid increased from 0.3% in 1991 to 2.6% in 2003. ESBL-producing Gram-negative isolates were detected in 3.2% of 6421 isolates from 42 ICUs and 21 non-ICU sites in the United States (*ICAAC C2-38, C2-46*).

In addition to infection control lapses and number of ventilator days, prior administration of third-generation cephalosporins, aminoglycosides, or trimethoprim-sulfamethoxazole were each associated with an increased risk of infection with ESBL-producing organisms. Ninety-five percent of isolates carried a mobile DNA element with a sulfonamide-resistance gene (*ICAAC K-717*).

In general, the most reliably effective antibiotics in the treatment of infection due to ESBL-producing Gram-negative bacilli are the fluoroquinolones and carbapenems. Thus, a retrospective analysis of 133 patients with bloodstream infection due to ESBL-producing *E coli* or *K pneumoniae* found that the 30-day mortality was 16% in those treated with either a carbapenem or ciprofloxacin, while it was 55% in those treated with a blood spectrum cephalosporin with or without an aminoglycoside. A separate retrospective study found that treatment of infections due to a ceftazidime-resistant *K pneumoniae* with another third-generation cephalosporin was associated with poor outcome. Combination therapy with a fluoroquinolone, but not an aminoglycoside, was associated with improved outcome (*ICAAC K-720, K-716*).

While third-generation cephalosporins are ineffective in the treatment of these infections, the role of cefepime, a putative fourth-generation cephalosporin, remains incompletely understood. Four papers dealt with this issue:

- A retrospective review of 8 patients who received cefepime for treatment of infections caused by ESBL-producing bacteria found that 6 experienced bacterial eradication and either clinical cure (5) or improvement (1). One patient experienced reinfection 2 weeks after completion of therapy. One of the 2 failures was infected at baseline with a cefepime-resistant organism (*IDSA 295*).
- Cefepime was used to treat 21 episodes of infection due to ESBL-producing *E aerogenes*, while a carbapenem was used in 23 episodes. Clinical improvement was observed in 62% and 70% ($P < .05$), respectively. Bacteriologic eradication was achieved in 14% of the cefepime and 22% ($P = .437$) of the carbapenem recipients (*ICAAC K-718*).
- A retrospective analysis of infections with an ESBL-producing *E aerogenes* found similar outcomes in 23 patients treated with a carbapenem and 21 who received cefepime (*ICAAC K-718*).
- Treatment of infection due to *E cloacae* with cefepime yielded good clinical results when the cefepime MIC was < 2 mcg/mL. ESBLs were, however, present in isolates with MICs as low as 4 mcg/mL (*ICAAC K-719*).

Cumulatively, these reports suggest that infections due to ESBL-producing Gram-negative bacilli may often be successfully treated with cefepime, provided that the MIC of the pathogen is < 2 mcg/mL. Since this value is well below the NCCLS breakpoint for susceptibility/resistance, most clinicians may not be able to make this distinction based on routine reports from their microbiology laboratory.

***Acinetobacter***

Risk factors for colonization by *Acinetobacter baumannii* were reported in separate studies to be associated with cephalosporin or carbapenem use. An important risk factor for infection due to carbapenem-resistant *A baumannii* was colonization density, defined as the mean number of culture-positive sites/total sites sampled (*ICAAC K-707, 708, K-710*).

Seven of 8 patients infected with multidrug-resistant *A baumannii* were successfully treated with IV colistin, although 6 had an increase in serum creatinine concentration of > 0.5 mg/dL (*ICAAC K-712*).

***Enterobacter***

In one case of *E cloacae* bacteremia, imipenem sus-

ceptibility did not predict diminished ertapenem susceptibility (*IDSA 227*).

### *Klebsiella*

Transferable plasmid-mediated quinolone resistance associated with the *qnr* gene, associated with low-level ciprofloxacin resistance, was found to be widely distributed in clinical strains of *K pneumoniae* in the United States. The activities of gatifloxacin, levofloxacin, gemifloxacin, and moxifloxacin each have MICs similar to ciprofloxacin against *qnr E coli* transconjugants. Additional chromosomal resistance in donor strains was associated with higher-level resistance to all quinolones tested (*ICAAC C1-605, C2-98*).

### *P aeruginosa*

The incidence of carbapenem resistance in *P aeruginosa* rose from 10% to 15% over 10 years at the University of Pennsylvania. This increase did not correlate with carbapenem use, suggesting that other agents may play a role in driving this resistance (*ICAAC C2-1964*).

Piperacillin/tazobactam and levofloxacin were synergistic or additive in vitro against 88% of 100 *P aeruginosa* isolates. Twenty-one of 42 (50%) isolates initially resistant to piperacillin/tazobactam became susceptible to it after addition of levofloxacin. The comparable result with 58 levofloxacin-resistant strains was 29% "conversion." In a result that I would have considered unexpected, in vitro synergy between gatifloxacin and ciprofloxacin was identified against 52% of 31 strains of ciprofloxacin-resistant *P aeruginosa*. It was speculated that gatifloxacin may inhibit efflux of ciprofloxacin (*IDSA 230, 229*).

### *Vibrio vulnificus*

Between 1991 and 2001, 65 patients in California were reported to have *Vibrio vulnificus* infection, and 40 (62%) died. Ninety-one percent presented with primary septicemia, and 89% of those reported consumption of raw oysters, all of which originated in the Gulf of Mexico (when origin was known). The sale of raw oysters harvested from the Gulf of Mexico from April 1 to October 31 is now restricted in California unless the oysters are appropriately treated with a process validated to reduce *V vulnificus* to nondetectable levels (*ICAAC L-181*).

## Urinary Tract Infection

In a randomized trial with prolonged follow-up involving 379 women with uncomplicated cystitis, ciprofloxacin 250 mg b.i.d. for 3 days was superior to amoxicillin/clavulanate 500 mg b.i.d. for 3 days. This was true even in women infected with bacterial strains susceptible to amoxicillin/clavulanate. Although the usual practice in the United States is to treat for only 3 days, a meta-analysis of randomized trials found that antibiotic treatment of uncomplicated urinary tract infection for 5-7 days achieves higher bacterial eradication rates (RR, 1.28; 95% CI, 1.05-1.56) at the cost of more adverse events. There was no difference with regard to symptom resolution (*ICAAC L-264, ICAAC L-261*).

Greater than 90% clinical and bacteriological cure was achieved in all treatment groups among 62 women with uncomplicated *E coli* cystitis randomized to treatment with either ciprofloxacin for 3 days, nitrofurantoin for 7 days, or a single dose of fosfomycin. Ciprofloxacin and fosfomycin, but not nitrofurantoin, each reduced vaginal and rectal *E coli* prevalence. Antibiotic resistance among rectal *E coli* arose only in 1 patient who had received ciprofloxacin, and in that case, it was transient (*ICAAC L-265*).

Antibiotic resistance is, nonetheless, increasing in frequency among urinary pathogens. A survey of 890 outpatient urinary *E coli* isolates from across the United States and Canada found that 38% were resistant to ampicillin, 23% to trimethoprim/sulfamethoxazole, 6.9% to levofloxacin, and 1.8% to nitrofurantoin. In a case-control study, risk factors for ciprofloxacin-resistant *E coli* urinary tract infection were found to be recurrent infections and, unsurprisingly, prior receipt of quinolones (*IDSA 226, ICAAC C2-267, C2-94*).

A cohort of 171 otherwise healthy nonpregnant patients with community-onset acute uncomplicated pyelonephritis was treated with orally administered ciprofloxacin for 7 days. Blood cultures were positive in 16.5%; 99% of all infections were due to *E coli*. Bacterial eradication and clinical cure were each 94%-95% when assessed 5-9 days post-treatment. The clinical success rate in bacteremic patients was 95% (*ICAAC L-262*).

Localization of the site of infection within the urinary tract is more complicated in males than in females because the prostate must be considered in the former. Thirty-three febrile adult males with urinary tract infection underwent scanning with radioactive indium-tagged leukocytes. Thirteen of 14 with clinical evidence of acute prostatitis had uptake in the prostate; 1 had it in the kidneys. Of the 6 with a clinical diagnosis of acute pyelonephritis, 3 had renal and 3 had prostatic uptake. Twelve of 13 with clinically undefined site of infection had prostatic uptake, and 1 had renal uptake. Rectal examination had 46% sensitivity, 80% specificity, 93% positive predictive value, and 21% negative predictive value for the diagnosis of acute prostatitis. The comparable figures for flank examination were 60%, 89%, 50%,

and 92%, respectively. Half the patients with flank tenderness had acute prostatitis. These findings demonstrate the limited accuracy of physical examination in site localization of urinary infection in males (*ICAAC L-259*).

## Mycobacterial Infections

### *Mycobacterium tuberculosis*

The introduction of TNF-blocking agents in the treatment of rheumatoid arthritis, Crohn's disease, and other inflammatory disorders has been associated with an increased risk of fungal and mycobacterial infections. Examination of the FDA Adverse Event database identified 574 reports of granulomatous infection associated with the use of etanercept or infliximab, occurring at frequencies of 494 out of 36,5000 vs 80 out of 150,000 ($P < .001$), respectively. Tuberculosis was most frequently reported, followed by histoplasmosis (*ICAAC B-1521*).

A single case of laryngeal tuberculosis resulted in transmission to 133 contacts, 5 of whom developed active tuberculosis. The apparent transmission rate to close contacts was 68%. In New York City, the mortality rate in patients with tuberculous meningitis decreased from 75% in 1992 to 42% in 2001. Among HIV-infected patients, mortality decreased from 86% to 67% (*ICAAC l-957, L-955*).

Routine monitoring of serum hepatic transaminases is not currently recommended in patients receiving INH for treatment of latent tuberculosis, except in patients at increased risk of hepatotoxicity. However, in patients with latent TB undergoing monthly evaluations, the incidence of INH-associated hepatitis (AST or ALT > 3 times normal) was 0.8% and was asymptomatic in 72 of 79 (91%). Twenty-seven of the 72 (38%), representing an overall incidence of 3 per 1000, had further increases in hepatic transaminases to > 5 times normal, with none ever developing symptoms. The only independent risk factor for hepatoxicity was increasing age. These results suggest that routine transaminase monitoring may be warranted in INH recipients (*IDSA 407*).

In a randomized trial involving patients with cervical tuberculous lymphadenitis, 12 months of therapy (2HERZ/10HRE) appeared to be superior to 6 months (2HERZ/4HRE) (*ICAAC L-954*).

Moxifloxacin was highly active in a murine model of tuberculosis, being more potent than isoniazid. In addition, in patients with active pulmonary tuberculosis, moxifloxacin and INH (each given alone) had comparable early bactericidal activity as defined as the decrease in CFU/mL of sputum at day 5 (*ICAAC B-1035, IDSA 405*).

Mycobacterial 16S rRNA was detected in 5 of 10 sarcoid tissue specimens and in none of 10 controls. In 3 of the 5, rpoB sequences were also identified. Sequencing suggested that the DNA detected was from a novel variant of *M tuberculosis* (*IDSA 416*).

### Mycobacteria Other Than Tuberculosis (MOTT)

Linezolid, levofloxacin, and moxifloxacin were active in vitro against *M kansasii* (*ICAAC E-1711*).

Outbreaks of skin and soft-tissue infections due to *M abscessus* occurred in individuals who received cosmetic injections by unlicensed personnel, as well as in others who had undergone acupuncture (*ICAAC K-1432, IDSA 845, 846*). ■

## CME Questions

5. **Patients isolated for methicillin-resistant *Staphylococcus aureus* infection or colonization experienced all but which one of the following negative consequences?**
   a. Preventable adverse effects, such as falls and pressure ulcers
   b. Greater dissatisfaction with their care
   c. Less documented care
   d. Greater hospital mortality

6. **Which of the following regimens have been shown by randomized trial to be of benefit for children with hematogenous suppurative arthritis?**
   a. Dexamethasone, without antibiotics
   b. A single dose of dexamethasone, with antibiotics
   c. Dexamethasone for 4 days, with antibiotics
   d. A single intra-articular injection of dexamethasone, with intravenous antibiotics
   e. No randomized trials have shown additional benefit of dexamethasone for suppurative arthritis.

7. **Which of the following is found susceptible to the polymyxin antibiotics ?**
   a. *Burkholderia cepacia*
   b. *Staphylococcus aureus*
   c. *Escherichia coli*
   d. *Proteus mirabilis*

**Answers:** 5(d); 6(c); 7(c)

## In Future Issues:

**New Perspectives on CVC Catheter Infections**

# UPDATES

By Carol A. Kemper, MD, FACP

## The Softer Side of Fluoroquinolones

**Source:** Johnstone TBC, et al. *Nature Medicine*. 2004;10:31-32.

Observing that some fluoroquinolones are associated with a lower incidence of seizures and anxiety, pharmacologists from California and the United Kingdom successfully modified norfloxacin to provide enhanced anxiolytic properties in rats without being overly sedating. Norfloxacin typically acts as an antagonist of the neurotransmitter γ-aminobutyric acid (GABA) in the brain, at the α receptor site. By modifying the parent compound at the R6 and R7 positions, Johnstone and associates came up with a variety of compounds that enhanced the action of GABA at the receptor complex site. One compound in particular, "compound 4," induced anxiolytic effects in rats similar to diazepam, with about one-tenth the potency. Unlike diazepam, no sedative or depressant CNS effects were identified. Because fluoroquinolones are structurally distinct from other agents with activity against the GABA receptor site, Johnstone et al hope these or other fluoroquinolone derivatives may provide a unique and highly selective way to target the GABA receptor. ■

## Cycloserine for Phobics?

**Source:** Pilcher HR. Society for Neuroscience Annual Meeting. November 2003.

Earlier studies have shown that D-cycloserine (DCS), a drug occasionally used to treat tuberculosis, allowed rats to overcome previously learned fears. Behavioral researchers reported in November that DCS was successfully used in treating patients with acrophobia. Thirty acrophobics were treated with DCS plus virtual reality behavioral modification, with a 50% reduction in anxiety and fear, compared with a 10% reduction using behavioral modification alone. Two sessions with DCS were equivalent, in terms of being able to successfully ride in an elevator or drive over a bridge (in virtual reality), to 8 sessions without the drug. Pilcher and colleagues hope that DCS will get phobics through the first training sessions, if nothing else. Apparently, the fear associated with the behavioral modification alone is sufficient to cause many patients to drop out or refuse further therapy. ■

## 115-Year-Old Smallpox Scabs—A Literary Find

**Source:** ProMED-mail post. January 2, 2004. promed@promedmail.org.

A librarian at the Sante Fe Fogelson College Library made the surprise discovery of a sealed envelope containing what appear to be 115-year-old smallpox vaccination scabs. The enveloped was labeled "scabs from vaccination of W.B. Yarrington's children," with the signature W.D. Kelly, and was found tucked between the pages of an 1888 Civil War medical text written by Kelly. After doing a quick literature search, the librarian discovered that Kelly had done research on childhood smallpox vaccination in the 1880s. She decided not to open the envelope. How the book made it to the library remains a mystery. Although the librarian initially inquired whether the Civil War Medicine Museum in Maryland would be interested in the specimens, the FBI quickly became involved. The scabs have since carefully made their way to the smallpox laboratory at the CDC in Atlanta. Based on the information on the envelope, the scabs were presumably obtained from someone variolated with smallpox virus, a common technique used to induce immunity in those days (first used in the United States by George Washington on troops during the Revolutionary War).

The hope is that the specimens may yield sufficient genetic material to shed light on the evolution of smallpox and vaccinia virus in the United States (vaccinia is a related but genetically distinct orthopox virus of uncertain origin, presently used for vaccination). It is believed (theoretically) possible to isolate smallpox virus, or at least genetic material, from well-preserved specimens, although past attempts have been fruitless. In the 1960s the WHO reportedly isolated variola virus from 13-year-old smallpox scabs. Analysis of tissues taken from the mummified corpse of a smallpox victim who died in Kentucky in the 1880s was unsuccessful. Similarly, although smallpox-like particles were visualized in the pox-like lesions of a mummified 16th century Italian child, no intact genetic material could be detected. The CDC intends to analyze the Fogelson College library samples sometime this spring. ■

## Positive PPDs Due to *M marinum* Infection

**Source:** Lewis FM, et al. *Clin Infect Dis*. 2003;37:390-397.

*Mycobacterium marinum*, originally isolated from dead fish in 1926, is a well-recognized cause of soft-tissue infection in persons with contact with swimming pools and fish tanks. Recent efforts to enhance chlorination of public pools and spas has decreased the risk from these sources, but the organism remains ubiquitous in aquatic environments, including both fresh and brackish waters and fish tanks. Lewis and associates reviewed 8 cases of *M marinum* soft-tissue infection, 6 of which had a positive culture, one of which had characteristic skin lesions and a positive smear, and one of which had characteristic skin lesions and fish tank exposure. Six patients had cutaneous disease, and 2 patients had deeper infection, including tenosynovitis in one and lymphadenitis in the other. Three patients had significant underlying disease, including rheumatoid arthritis (on plaquenil), melanoma and psoriasis (on prednisone), and diabetes mellitus.

Six patients (including 5 with cutaneous disease and one patient with tenosynovitis) responded to 3-6 months of chemotherapy, with or without debridement. Treatment consisted of clarithromycin and ethambutol in 4 patients, and ethambutol and rifampin in 2 patients. (The 2 individuals lacking confirmatory cultures responded to treatment within 2-6 months). Of the remaining 2 patients, the patient with rheumatoid arthritis eventually responded to 14 months of ethambutol and rifampin. The other patient with psoriasis who was receiving corticosteroid therapy failed to respond to ~2 years of treatment with clarithromycin, ethambutol, rifampin, and amikacin, despite repeated attempts at debridement and excision of infected lymph nodes.

Lewis et al suggest that current recommendations more strongly stress the avoidance of fish tanks and suspect waters for persons with open wounds or immune suppression. While no controlled trials exist, treatment with at least 3 agents (clarithromycin, ethambutol, and rifampin) should be considered for initial therapy. The duration of therapy is variable but should be continued for a minimum of 3-4 months, and for at least 1-2 months after resolution of clinically apparent disease.

Interestingly, all 6 patients tested had tuberculin skin tests positive at > 10 mm (2 had reactions > 15 mm). Although it is known that nontuberculous mycobacterial infections can result in positive tuberculin skin test reactions, we don't usually think of this when confronted with a patient with a positive PPD. One report found that patients with *M marinum* infection may have positive skin tests up to 60% of the time. Lewis et al found that 100% of their patients with *M marinum* had positive skin tests. Treatment for latent TB may not be indicated in such patients, especially if they lack risk factors for TB. ■

## Cost-Effectiveness of Influenza Treatment

**Source:** Rothberg MB, et al. *Ann Intern Med*. 2003;139:321-329.

Using decision analysis, the cost-effectiveness of rapid diagnostic testing and antiviral therapy for influenza-like illness was evaluated in older adults (older than 65). The model was based on several key assumptions, including that neuraminidase inhibitors would decrease hospitalizations by 33%, along with a comparable reduction in complications and antibiotic use, although zanamivir would be somewhat less effective than oseltamivir because ~50% of older adults would have difficulty loading and administering the medication. In addition, it was assumed that amantadine and rimantadine were less effective because they would not reduce hospitalization and are only effective against influenza A virus. The model was not sensitive to the prevalence or severity of medication side effects.

Not surprisingly, in adults at greatest risk for influenza—unvaccinated, institutionalized, nursing home residents, etc—empiric treatment with oseltamivir without diagnostic testing was the most cost-effective strategy. In patients at lower risk (eg, those who have been vaccinated), rapid diagnostic testing followed by appropriate therapy with oseltamivir was the most cost-effective approach. Empirical amantadine was less cost effective in either circumstance, but could be used if patients had to pay for drug out of their own pocket and couldn't afford the more expensive agent. (This sounds a bit like backward logic to me: Oseltamivir is cost-effective as long as someone else is paying for it?)

While these conclusions largely make sense, one wonders how the model would perform in the current year when the predominant circulating strain of influenza virus (eg, A/Fujian/411/2002) is not included in (although may be partially covered by) the current vaccine. ■