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INSIDE

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Kingella kingae Skeletal Infections in Children

ABSTRACT & COMMENTARY

By Hal B. Jenson, MD, FAAP

Chair, Department of Pediatrics, Director, Center for Pediatric Research, Eastern Virginia Medical School and Children's Hospital of the King's Daughters

Dr. Jenson is on the speaker's bureau of Merck.

Synopsis: Kingella kingae *is increasingly recognized as a cause of skeletal infections among children. The first reported outbreak of* K. kingae *disease, among 3 children at a childcare center, is described.*

Source: Kiang KM, et al. Outbreak of Osteomyelitis/Septic Arthritis Caused by *Kingella kingae* Among Child Care Center Attendees. *Pediatrics* 2005;116:e206-213.

TWO DEFINITE (CULTURE-CONFIRMED), AND ONE PROBABLE, cases of *K. kingae* invasive disease were reported in Minnesota in October 2003, among children attending the same toddler classroom of a childcare center. The first case was a 21-month-old boy diagnosed with femoral neck osteomyelitis and suppurative arthritis of the hip. The temperature was 103º F, WBC 17,200 cells/mm^3, ESR 51 mm/hr, and CRP < 0.5 mg/dL (normal). Synovial and bone cultures showed *K. kingae* after 3 days of incubation. He was successfully treated with 3 weeks of intravenous piperacillin-tazobactam, followed by 2 weeks of oral amoxicillin-clavulanate. The second case was a 20-month-old girl who had recently completed a course of amoxicillin-clavulanate for otitis media. She developed ankle and subtalar suppurative arthritis.

The temperature was 101.6º F, WBC 7700 cells/mm^3, and ESR 38 mm/hr. *K. kingae* was cultured after 4-5 days

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of incubation. She was successfully treated with 4 weeks of oral amoxicillin-clavulanate. The third case was a 17-month-old boy diagnosed with otitis media and reactive arthritis. The temperature was 102ºF, WBC 12,500 cells/mm^3, and the CRP 1.27 mg/dL (mildly increased). He was treated initially with oral amoxicillin. His limp continued, and MRI 16 days later revealed distal tibial osteomyelitis. No cultures were obtained.

All 3 children had preceding or concurrent symptoms of upper respiratory tract infection. Oropharyngeal cultures from 115 children (94%) and 29 staff (97%) at the childcare center showed that 15 children (13%) were colonized with *K. kingae*, including 9 (45%) children in the classroom of the 3 affected children. No staff or children < 16 months of age were colonized. All 9 children who were colonized were given rifampin prophylaxis using the regimen recommended for meningococcus (4 doses, every 12 hours for 2 days); 3 (33%) remained positive on reculture 10--14 days later.

COMMENTARY

The past 15 years has seen the dramatic decline of *Haemophilus influenzae* type b infections, including skeletal infections resulting from universal vaccination with the conjugate vaccine. Use of the conjugate pneumococcal vaccine will have the same impact on *Streptococcus pneumoniae* infections. In the milieu of these seismic changes, less dramatic changes are also occurring, including the increasing recognition of *K. kingae* as a cause of childhood invasive disease. Conjugate vaccines not only reduce the incidence of invasive disease, but also decrease the rate of nasopharyngeal carriage. This effect may provide an opportunistic niche for nasopharyngeal carriage of less virulent organisms such as *K. kingae*.

This is the first reported outbreak of *K. kingae* infection, and emphasizes the underappreciation of *K. kingae* as a cause of childhood skeletal infections. This report offers several insights into pediatric *K. kingae* infections. *K. kingae* frequently colonizes the oropharynx and is most likely transmitted via upper respiratory tract secretions, saliva, and potentially oral contact with contaminated fomites. This cluster supports the oropharyngeal transmission of the organism. As in this outbreak, most reported cases are among children 6-24 months of age and occur in the fall and winter months, perhaps reflecting close quarters during the colder months. Skeletal infections caused by *K. kingae* present with low-grade fever and only modest elevation of WBC, ESR, and CRP but are clinically indistinguishable from those caused by *Staphylococcus aureus* and group A streptococcus, the most common causes of childhood skeletal infections. Culture is required for confirmation. *K. kingae* is susceptible to many antimicrobial agents, with low MICs to penicillin, azithromycin, and rifampin. The attempt to eliminate nasopharyngeal carriage was an interesting approach; unfortunately, it was only modestly successful (67%). It may be that the regimen used for *H. influenzae* (4 doses, every 24 hours for 4 days) would be more successful. The impact of prophylaxis on invasive disease is unknown. ■

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Metronidazole: Still First-Line Therapy for Antibiotic-Associated Colitis?

ABSTRACT & COMMENTARY

By Robert Muder, MD

Hospital Epidemiologist, Pittsburgh VA Medical Center

Dr. Muder does research for Aventis and Pharmacia.

Synopsis: *In a prospective, observational study of 207 patients with* Clostridium difficile *colitis treated with metronidazole, 22% had symptomatic colitis for > days, and 28% had a relapse within 90 days.*

Source: Musher DM, et al. Relatively Poor Outcome After Treatment of *Clostridium difficile* Colitis With Metronidazole. *Clin Infect Dis*. 2005;40:1586-1590.

MUSHER AND COLLEAGUES FOLLOWED 207 PATIENTS with *C. difficile* colitis treated with appropriate (at least 1.5 gm/day) doses of metronidazole for at least 7 days. All patients had a positive stool ELISA assay for *C. difficile* toxin. Fifty percent of patients had a clinical cure within 10 days of the start of treatment with no recurrence. Twenty eight percent of patients had initial resolution of symptoms but suffered a recurrence within 90 days. Twenty-two percent of patients were refractory to treatment, defined as symptomatic after > 10 days of metronidazole therapy. There was no relationship between response to metronidazole therapy and quantity of antibiotics patients received in the 6 weeks preceding onset of colitis. The preceding use of cefepime or vancomycin was, however, significantly associated with metronidazole failure. Susceptibility testing to metronidazole was not performed during this study, but subsequent testing of 18 strains isolated from the hospital showed that none were metronidazole resistant.

COMMENTARY

C. difficile colitis is a frequent complication of antimicrobial therapy. Clinical severity is variable, ranging from loose stools to fulminant colitis with toxic megacolon. Disease is more frequent and more severe in patients with advanced age and serious co-morbid conditions. Historically, *C. difficile* colitis has responded equally well to treatment with either metronidazole or oral vancomycin, with clinical response rates of > 90%; approximately 20% of successfully treated patients suffer one or more relapses.[1] Relapse is associated with low levels of specific immunoglobulin directed against *C. difficile* toxin.

In the past few years, there is evidence that the epidemiology and clinical presentation of *C. difficile* colitis is changing. Several centers report an increase in both the frequency and severity of *C. difficile* colitis. A regional medical center in Quebec noted an abrupt 4-fold increase in the incidence of *C. difficile* colitis beginning in 2003.[2] The proportion of cases with complications (megacolon, perforation, shock, colectomy) increased from 7% to 18%. The proportion of patients suffering a recurrence increased from 21% to 47%.[3] During the same period, the University of Pittsburgh Medical Center reported a more than doubling of the incidence of nosocomial *C. difficile* colitis and an increase in the number of cases complicated by colectomy or death.[4]

The reasons for this apparent change in the frequency and clinical presentation of *C. difficile* colitis are not entirely clear. Several reports implicate increasing use of newer quinolones that have significant activity against anaerobes.[4,5] There is also evidence that a change in *C. difficile* toxin production may play a part in more severe disease. In addition to the 2 major toxins, A and B, some *C. difficile* strains possess a binary toxin, which is an actin specific adenosine diphosphate ribosyltransferase related to toxin E of *C. perfringens*. Preliminary evidence suggests that the presence of binary toxin may be related to increased severity of colitis.[6]

Optimal treatment for *C. difficile* colitis remains an area of uncertainty. Resistance of clinical isolates to the metronidazole and vancomycin is rare. A limited number of randomized trials comparing metronidazole and vancomycin have shown the 2 agents to be comparable. Critically ill patients, however, were excluded. Until additional data or more effective treatments become available, the recommendations provided by Dr. Gerding in an accompanying editorial[7] appear to be eminently reasonable. Patients with moderate illness should be treated with metronidazole. Patients with total leukocyte counts of > 20,000 are at high risk for complications and should be treated with oral vancomycin. Patient developing ileus or megacolon

should be treated with intravenous metronidazole and enteral vancomycin (via nasogastric tube and/or enema), in addition to aggressive supportive therapy and early surgical consultation for possible colectomy. ■

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Tigecycline (Tygacil)

By Jessica C. Song, MA, PharmD, and Hyunah Eom, PharmD

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Dr. Song and Dr. Eom report no consultants, stockholders, speaker's bureaus, research, or other financial relationships with companies having ties to this field of study.

OVER THE PAST DECADE, THERE HAS BEEN GROWING concern about the magnitude of antimicrobial resistance, particularly among gram-positive organisms such as penicillin-resistant *Streptococcus pneumoniae*, methicillin-resistant staphylococci, and vancomycin-resistant enterococci.[1] In light of the fact that at least 3 cases of vancomycin-resistant *Staphylococcus aureus* infection have been described in the United States, the need for new antimicrobial agents is greater than ever.[2,3] A recent report highlighted the slowing of antibiotic drug development expansion, as new antimicrobial agents comprised 6 of 506 drugs under development by major biotechnology and pharmaceutical companies.[1] Agents such as daptomycin, linezolid, and quinupristin/dalfopristin are available for the management of drug-resistant gram-positive infections, but resistance to these agents has been reported,[4,5] and serious adverse effects such as myopathy,[6] myelosuppression,[7] and arthralgia[8] have been associated with the use of these drugs.

Although the tetracycline class of antimicrobials has been in place for 60 years, widespread development of resistance has significantly limited the use of tetracyclines in the treatment of many infections.[1] Structural manipulations of the tetracycline molecule resulted in the development of a more stable class of compounds, the glycylcyclines.[1] Reversible binding of glycylcyclines to the 30S subunit of the bacterial ribosome occurs following entry into the bacterial cell through either passive diffusion or energy-dependent pathways. This reversible binding blocks the incorporation of transfer RNA into the ribosome and, ultimately, disrupts protein synthesis.[9] Tigecycline, the first glycylcycline agent to be marketed in the United States, was approved by the FDA on June 16, 2005, for use in the treatment of adults with complicated skin/skin structure infections and complicated intra-abdominal infections.[1] This article will: 1) review the pharmacology, pharmacokinetics, and FDA indications of tigecycline, 2) review its drug interactions, dosage, and resistance patterns, and 3) review the safety and efficacy of tigecycline.

Spectrum of Activity

Tigecycline exhibits in vitro activity against the majority of gram-positive and gram-negative aerobes, as well as anaerobes and some atypical organisms.[1] Table 1 lists the minimum concentrations required to inhibit 90% of clinically encountered bacteria (MIC90), as well as the FDA-established MIC breakpoints for susceptibility to tigecycline for selective organisms. Of note, tigecycline has limited activity against strains of *Proteus mirabilis*, Providencia, *Pseudomonas aeruginosa*, *Serratia marcescens*, and *Legionella pneumophila*.[1]

Pharmacologic/Other Clinical Properties of Tigecycline

Table 2 summarizes the mechanism of action,

spectrum of activity, FDA indications, pharmacokinetics, dosing/administration, contraindications, adverse effects, drug interactions, resistance patterns, and cost of tigecycline.

Clinical Efficacy of Tigecycline

A review of the literature showed that most clinical studies to date have been presented as posters at various conferences. A pooled analysis of 2 Phase III randomized, double-blind, active-controlled, multinational, multicenter studies compared the efficacy of tigecycline with that of combined therapy with vancomycin 1 g IV q 12 h/aztreonam 2 g IV q 12h in hospitalized patients with complicated skin and skin structure infections.[10,12] Patients randomized to receive tigecycline were administered a 100 mg IV loading dose, followed by 50 mg IV q 12h. Patients with complicated deep soft tissue infections including wound infections and cellulitis (10 cm, necessitating surgery/drainage or with complicated underlying disease), infected ulcers with evidence of an acute infection, infected burns, infected human, or animal bites, major abscesses (complicated or extensive), superficial infections, or abscesses with a high risk of infection due to gram-negative or anaerobic pathogens, and infected ulcers were enrolled in the studies. Deep soft tissue infection with cellulitis represented the most common diagnosis. The primary end point was the clinical response at the test of cure visit in the clinically evaluable (n = 1562) and clinical modified intent-to-treat (n = 1911) subjects. Clinical cure rates observed with tigecycline and vancomycin/aztreonam were 86.5% and 88.6% (*P*-value not reported), respectively, in clinically evaluable patients. Clinical cure rates observed with tigecycline and vancomycin/aztreonam were 79.7% and 81.9% (*P*-value not reported), respectively, in the clinical modified intent-to-treat patients.

A pooled analysis of 2 Phase III randomized, double-blind, active-controlled, multinational, multicenter studies compared the efficacy of tigecycline with that of imipenem 500 mg IV q 6h in hospitalized patients with complicated intra-abdominal infections.[10,13] Patients randomized to receive tigecycline were administered a 100 mg IV loading dose, followed by 50 mg IV q 12h. Patients with complicated intra-abdominal infections, including appendicitis (most common diagnosis), cholecystitis (second most common diagnosis), intra-abdominal abscess (third most common diagnosis), perforated intestine, diverticulitis, gastric/duodenal perforation, and peritonitis were enrolled in the studies. The primary end point was the clinical response at the test of cure visit in the clinically evaluable (n = 1908) and clinical modified intent-to-treat (n = 2282) subjects. Clinical cure rates observed with tigecycline and imipenem were 86.1% and 86.2% (*P*-value not reported), respectively, in clinically evaluable patients. Clinical cure rates observed with tigecycline and imipenem were 80.2% and 81.5% (*P*-value not reported), respectively, in the clinical modified intent-to-treat patients.

At present, 4 ongoing Phase III clinical trials are assessing the efficacy of tigecycline in hospitalized patients with infections caused by antibiotic-resistant gram-negative bacteria (*Acinetobacter baumanii*, Enterobacter spp., *Klebsiella pneumoniae*), infections caused by vancomycin-resistant Enterococci or methicillin-resistant Staphylococci, and in patients with community-acquired pneumonia or nosocomial pneumonia.[14]

There is a crucial need for well-tolerated antimicrobial agents that are effective against resistant organisms, such as vancomycin-resistant enterococci, staphylococci with reduced susceptibility to vancomycin, and resistant gram-negative pathogens. Currently, 4 antimicrobial agents, daptomycin, linezolid, quinupristin-dalfopristin, and tigecycline are available for use in the treatment of infections caused by drug-resistant gram-positive pathogens. Oral formulations of daptomycin, quinupristin-dalfopristin, and tigecycline are not available, and administration is limited to the IV route. This represents a potential disadvantage compared with linezolid, which is available as parenteral and oral formulations. However, compared with the current agents that are available for use in the treatment of infections caused by drug-resistant gram-positive pathogens, tigecycline has a superior side effect profile, as nausea and vomiting were the most commonly reported adverse events in clinical trials. Although early results from Phase III clinical trials are promising, ongoing clinical trials will help further define the potential role of tigecycline.

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Table 1

In Vitro Activity of Tigecycline Against Selective Organisms

Organism (mcg/mL) Breakpoints	MIC_{90} (mcg/mL)	FDA-Established MIC	
R		S	I
S. aureus (OXA[6])	0.25-0.5	≤ 0.5	–
S. aureus (OXA[R])	0.25-1	≤ 0.5	–
S. aureus (VAN[I])	0.5	≤ 0.5	–
E. faecalis	0.13-0.5	≤ 0.25	–
E. faecalis (VAN[R])	0.13-0.5	–	–
E. faecium	0.13-0.25	–	–
E. faecium (VAN[R])	0.13	–	–
Group A Streptococci	0.06-0.25	≤ 0.25	–
Group B Streptococci	0.06-0.25	≤ 0.25	–
E. Coli (non-ESBL) ≥ 8	0.25-1	≤ 2	4
E. Coli (ESBL) ≥ 8	0.5-1	≤ 2	4
E. Coli (CIP[R]) ≥ 8	1	≤ 2	4
K. pneumoniae (non-ESBL) ≥ 8	1-2	≤ 2	4
K. pneumoniae (ESBL) ≥ 8	1-2	≤ 2	4
K. oxytoca ≥ 8	1	≤ 2	4
C. freundii ≥ 8	2	≤ 2	4
E. cloacae ≥ 8	2	≤ 2	4
P. aeruginosa	16-32	–	–
C. pneumoniae	0.13	–	–
M. pneumoniae	0.25	–	–
B. fragilis ≥ 16	2	≤ 4	8
B. fragilis group ≥ 16	0.13-2	≤ 4	8
C. perfringens ≥ 16	0.25-1	≤ 4	8
Peptostreptococcus species ≥ 16	0.03-0.25	≤ 4	8

Table 2

Pharmacologic, Pharmacokinetic, Clinical Properties of Tigecycline[10]

Brand/Generic	Tygacil® (Tigecycline)
Classification	Glycylcycline
Mechanism of Action	Inhibits protein translation in bacteria by binding to the 30S ribosomal subunit and blocking entry of amino acyl tRNA
Spectrum of Activity	• Aerobic falcutative gram-positive microorganisms *Enterococcus faecalis* (vancomycin susceptible), *Staphylococcus aureus* (Methicillin-susceptible and -resistant), *Streptococcus agalactiae*, *Streptococcus anginosus* grp. (includes *S. anginosus*, *S. intermedius*, *S. constellatus*), *Streptococcus pyogenes* • Aerobic and falcutative gram-negative microorganisms -*Citrobacter freundii*, *Enterobacter cloacae*, *Escherichia coli*, *Klebsiella oxytoca*, *Klebsiella pneumoniae* • Anaerobic microorganisms -*Bacteroides fragilis*, *Bacteroides thetaiotaomicron*, *Bacteroides uniformis*, *Bacteroides vulgatus*, *Clostridium perfringens*, *Peptostreptococcus micros*
FDA Indications	• Complicated skin and skin structure infections attributable to *Escherichia coli*, *Enterococcus faecalis* (vancomycin-susceptible isolates only), *Staphylococcus aureus* (methicillin-susceptible and -resistant isolates), *Streptococcus agalactiae*, *Streptococcus anginosus* grp., *Streptococcus pyogenes*, and *Bacteroides fragilis* • Complicated intra-abdominal infections caused by *Citrobacter freundii*, *Enterobacter cloacae*, *Escherichia coli*, *Klebsiella oxytoca*, *Klebsiella pneumoniae*, *Enterococcus faecalis* (vancomycin-susceptible isolates only), *Staphylococcus aureus* (methicillin-susceptible isolates only), *Streptococcus anginosus* grp., *Bacteroides fragilis*, *Bacteroides thetaiotaomicron*, *Bacteroides uniformis*, *Bacteroides vulgatus*, *Clostridium perfringens*, and *Peptostreptococcus micros*

Pharmacokinetics	Half-life	Biliary/ fecal excretion	Recovered unchanged in urine	V_d (L)	Protein bound	Hepatic metabolism
	36h	59%	22% as total dose as unchanged tigecycline	500-700	71%-89%	Not extensive; glucuronide, N-acetyl metabolite, tigecycline epimer
How Supplied	Single-dose 5 mL glass vial containing 50 mg lyophilized powder for reconstruction					
Dosage	For skin/skin structure infections and intra-abdominal infections in patients 18 years and older: • Initial dose of 100 mg IV, followed by 50 mg IV every 12 hours infused over 30-60 minutes • Recommended duration of treatment for intra-abdominal infections: 5-14 days					
Dosage Adjustment	**Renal** No dosage adjustment required in renally impaired patients or in patients undergoing hemodialysis. **Hepatic** Severe hepatic impairment (Child Pugh C): Initial dose of 100 mg IV, followed by a maintenance dose of 25 mg IV every 12h					
Storage/Administration[11]	**Storage** • Prior to reconstitution, store vial at room temperature (20°to 25° (68° to 77°)) • Diluted IV infusion can be stored at room temperature for 6h and refrigerated (2° to 8° C (36° to 46° F)) for up to 24h **Administration** • Reconstitute with 5.3 mL of 0.9% sodium chloride (NS) for injection or 5% dextrose (D5W) injection • Withdraw 5 mL of reconstituted solution and add to a 100 mL D5W or NS bag (maximum concentration: 1 mg/mL) • Infuse over 30-60 minutes; GI symptoms may be reduced if the infusion is started after meals					
Contraindications	Previous hypersensitivity to tigecycline					
Precautions/Warnings	• In phase III studies, a small number of tigecycline-treated patients (monotherapy) developed sepsis/septic shock • Tigecycline is structurally related to tetracycline class antibiotics and may have similar adverse effects such as causing fetal harm when administered to a pregnant patient or may cause permanent teeth discoloration (last half of pregnancy, infancy, childhood up to age 8 years) • *Pseudomembranous colitis*					
Adverse Effects	Most frequently reported in Phase III clinical studies: • Nausea (29.5%) • Vomiting (19.5%) • Diarrhea (12.7%) • Injection site reactions (9%)					
Drug Interactions	• Monitor prothrombin time if tigecycline is co-administered with warfarin • Concomitant use of tigecycline with oral contraceptives may lessen the efficacy of oral contraceptives					
Pregnancy Category	• Pregnancy category D					
Resistance[1]	In laboratory studies, it has been difficult to generate mutations in bacteria engendering tigecycline resistance. It has been proposed that significant bacterial resistance in the clinical setting will not occur easily.					
Daily Cost[a]	Tigecycline (50 mg IV q 12) $90.46	Daptomycin (500 mg vial)[b] (4 mg/kg IV qd is usual dose) $111.90 per 500 mg vial	Quinupristin-Dalfopristin 500 mg IV q 8h (7.5 mg/kg IV q 8h; 67 kg) $286.56	Linezolid (IV) 600 mg q 12 $136.72	Linezolid (Oral) 600 mg q 12h $73.88	

[a]Cost of tigecycline accessed from Cardinal Health on August 1, 2005. The actual cost of tigecycline may be subject to variation, depending on contract-pricing and on quarterly reports from Novation. The cost of daptomycin was accessed from the Purchasing department at Santa Clara Valley Medical Center in November 2004, and may be subject to quarterly variation. The costs of quinupristin-dalfopristin, linezolid IV, and oral linezolid (outpatient) were accessed from the Purchasing department at Santa Clara Valley Medical Center in January 2005, and may be subject to quarterly variation. [b] Daptomycin is also available as a 250 mg vial. Reconstituted solution is stable for up to 48 hours if refrigerated.

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Invasion of the Probiotics: Iatrogenic *Saccharomyces cerevisiae* Fungemia

ABSTRACT & COMMENTARY

By Robert Muder, MD

Synopsis: *Three ICU patients receiving* Saccharomyces boulardii *(cerevisiae) therapy for treatment of* Clostridium difficile *colitis experienced fungemia. Review of 60 cases of* S. cerevisiae *fungemia reported in the literature found that risk factors included presence of a central venous catheter, intravenous or enteral alimentation, and receipt of* S. cerevisiae *as a probiotic.*

Source: Munoz, et al. *Saccharomyces cerevisiae* Fungemia: An Emerging Infectious Disease. *Clin Infect Dis*. 2005;40: 1625-1634.

Saccharomyces boulardii (RECENTLY RECOGNIZED as a strain of *S. cerevisiae* rather than a distinct species) is widely used as a probiotic for the treatment of diarrhea and for the prevention and treatment of *C. difficile*-associated colitis. Munoz and colleagues report 3 patients acquiring *S. cerevisiae* fungemia during a 2-week period in an intensive care unit. All 3 patients had undergone open heart surgery. All 3 developed *C. difficile*- associated colitis and received a commercial preparation of *S. boulardii* along with standard antimicrobial therapy. One of the patients had undergone placement of a mitral valve prosthesis. She had sustained fungemia and evidence of a valvular vegetation on echocardiogram. Molecular typing of the 3 clinical isolates showed them to be identical to the yeast isolated from the probiotic capsules.

Review of the literature identified a total of 60 cases of S. cerevisiae fungemia. Sixty percent of the patients were admitted to the ICU; 93% had a central venous catheter, 71% had received enteral or parenteral nutrition, and 43% had received probiotic *Saccharomyces* treatment.

COMMENTARY

S. boulardii (cerevisiae) has been shown in clinical trials to reduce the incidence of *C. difficile*- associated colitis and to reduce the frequency of relapse. In the laboratory, *S. boulardii* produces a protease that digests *C. difficile* toxins A and B;[1] this may be the mechanism of the clinical effect. *C. boulardii* does not, however, appear to affect the course of established *C. difficile* diarrhea.[2] The exact relationship between pro-

biotic use and fungemia is not entirely clear. A likely mechanism is inadvertent contamination of central catheters when the probiotic capsules are opened and administered via nasogastric tube.

This report and literature review demonstrates that, contrary to popular believe, administration of probiotics is not always benign. Patients who are critically ill, who have central catheters, or who are immunosuppressed should not received probiotic therapy. Although there are no clinical trials to guide therapy, *S. cerevisiae* is typically susceptible to amphotericin. Susceptibility to fluconazole and itraconazole is variable. Limited data suggests that most strains are likely to be susceptible to voriconazole.

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Inhibition of Daptomycin By Pulmonary Surfactant

ABSTRACT AND COMMENTARY

By Dean L. Winslow, MD

Chief, Division of AIDS Medicine, Santa Clara Valley Medical Center, Clinical Professor, Stanford University School of Medicine

Dr. Winslow is a consultant for Bayer Diagnostics and Pfizer/Agouron and is on the speaker's bureau of Pfizer/Agouron.

Synopsis: *Daptomycin specifically interacts with pulmonary surfactant and its antimicrobial activity is inhibited in a dose-dependent fashion by surfactant.*

Source: Silverman JA, et al. Inhibition of Daptomycin By Pulmonary Surfactant: In Vitro Modeling and Clinical Impact. *J Infect Dis*. 2005;191:2149-2152.

THE FDA HAS RECENTLY APPROVED DAPTOMYCIN FOR use in skin and skin-structure infections, but this antibiotic failed the test of non-inferiority in a trial of severe community-acquired pneumonia. In addition, preclinical in vivo animal model studies of daptomycin conducted by the sponsor had shown disappointing results in bronchial-alveolar pneumonia, but displayed good activity in hematogenous staphylococcal pneumonia.

Silverman and colleagues demonstrate that the in vitro antistaphylococcal activity of daptomycin was inhibited by the inclusion of small amounts of bovine surfactant in broth media with > 100 fold increase in MIC observed with as little as 10% surfactant concentration. The activity of ceftriaxone was unaffected in these same experiments. Silverman et al, in a nice complementary experiment, demonstrated calcium-dependent insertion of daptomycin into surfactant aggregates in vitro, consistent with its in vitro antibacterial mechanism of action.

COMMENTARY

Daptomycin is a new and important antibiotic in our arsenal to combat the emerging scourge of gram positive bacterial infections. Daptomycin is a lipopeptide antibiotic which exerts its bactericidal effect by a calcium-dependent insertion into and disruption of the functional integrity of the G+ plasma membrane, resulting in rapid loss of membrane potential, cessation of macromolecular synthesis, and cell death.[1]

The drug was approved by the FDA in 2003, for use in skin and skin-structure infections. Despite potent in vitro activity against *Streptococcus pneumoniae* (MIC_{90} 0.06 ug/mL), a phase 3 clinical trial in severe community-acquired pneumonia failed to achieve statistical non-inferiority to the ceftriaxone comparator arm. Pulmonary surfactant is a complex mixture of dipalmitoylphosphatidylcholine, phosphatidylglycerol, minor phospholipids, neutral lipids, and cholesterol which acts within alveoli to reduce surface tension and prevent alveolar collapse.[2] The experiments summarized above provide a nice explanation of these unexpected in vivo clinical trial results by demonstrating in vitro inhibition of the antibacterial effect of daptomycin by surfactant, and correlating this with calcium-dependent insertion of daptomycin into surfactant aggregates.

During the 4 decades I have been involved in clinical care of patients with infections and in drug development with several pharmaceutical companies, I never fail to be fascinated by the often poor correlation between in vitro activity of antimicrobials and in vivo activity. Some of the best-studied mechanisms of this discordance include bioavailability and metabolism which limit exposure of the pathogen to the drug, variable effects of protein binding (albumin, alpha-1-acid glycoprotein, etc.), physiochemical properties which limit diffusion of the drug into certain compartments, or ability of the drug to inhibit intraleukocytic pathogens. This paper adds another mechanism to this list.

Despite the limitation of daptomycin in treating patients with bronchial-alveolar pneumonia, I believe

daptomycin will be an important antibiotic in the treatment of the ever-increasing numbers of patients with either Beta lactam-resistant or vancomycin-resistant pathogens. While not officially approved for indications other than skin and skin-structure infections at this time, daptomycin's bactericidal action makes it an attractive option for the treatment of bacteremia and endocarditis caused by antimicrobial resistant pathogens.

References

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CME Question

3. Which infection is most characteristic of *Kingella kingae* infections among children?

a. Chronic bronchitis, sinusitis, and otitis media
b. Meningitis
c. Osteomyelitis and suppurative arthritis
d. Pneumonia
e. Folliculitis

Answer: 3.(c)

CME Objectives

The objectives of *Infectious Disease Alert* are:

•To discuss diagnosis and treatment of infectious diseases;

•To present current data regarding use of new antibiotics for commonly diagnosed diseases and new uses for traditional drugs;

•To present the latest information regarding the pros, cons, and cost-effectiveness of new and traditional diagnostic tests;

•To present prevalence/surveillance data for various diseases, such as AIDS, tuberculosis, malaria, and pneumonia; and

•To discuss new information regarding how infectious diseases (eg, AIDS) are transmitted and how such information can lead to the development of new therapeutic drugs. ■

In Future Issues:

Eradicating HIV Infection?

UPDATES

By Carol A. Kemper, MD, FACP

Clostridium sordellii Toxic Shock

MMWR. July 22, 2005; 54:1.

THE FDA HAS ISSUED A PUBLIC Health Advisory regarding the identification of 4 cases of toxic shock following medical abortion with Mifepristone (formerly RU-486) and intravaginal misoprostol in the United States. Two of the cases occurred in 2003, but the recent cases occurred in 2004 and 2005. Although 2 of the cases are still being investigated, at least 3 were associated with toxic shock and endometrial infection, secondary to *Clostridium sordellii*, an anaerobic spore-forming bacterium similar to *C. perfringens*. *C. sordellii* has most recently been described as a cause of toxic shock and sepsis in persons receiving contaminated orthopedic allografts. A fifth and fatal case of *C. sordellii* sepsis was reported in a Canadian women following medical abortion with Mifepristone and intravaginal misoprostol in 2001. Three of these cases were associated with intravascular hemolysis, hypotension, and leukocytosis, but were notable for a lack of fever.

While cases of toxic shock-like syndrome in obstetric patients are often related to *C. perfringens*, *C. sordellii* has also been previously described as a cause of severe and life-threatening endometritis and toxic shock in a variety of obstetric-related conditions, including spontaneous abortion, second trimester amniocentesis, septic abortion, as well as post-partum patients. Thus, its occurrence in the setting of medical abortion using RU-486 may not be too surprising. Cases of toxic shock and endometritis in the obstetric setting should receive empiric coverage with agents with anti-anaerobic activity against clostridial species, at least until culture data is available. The FDA has asked that suspect cases of toxic shock occurring postpartum or post-abortion be reported (www.fda.gov/medwatch/index.html). ■

What the Tsunami Brought to Cologne

Maegele M, et al. *Crit Care Med*. 2005; 33:1136.

PHYSICIANS AT THE MERHEIM Medical Center in Cologne, Germany, who provided care to German survivors from the Tsunami in Asia, provide an expansive guest list of microbial agents air-transported along with the victims. Maegele and colleagues describe the catastrophe from traumatic injuries, including infected wounds from contact with seawater, coral, and vegetation, which resulted in infection from vibrio spp and aeromonas; patients swept inland were also exposed to inland pools and swamps, with potential for infection from pseudomonas, aeromonas, legionella, chromobacterium, and leptospira. Patients were also in contact with fecally contaminated water and raw sewage, resulting in a variety of Gram negative infections.

Many victims were found to have wound infections with highly resistant bacteria, including MRSA, and about 20% of wound infections were due to a multiple drug resistant strain of *Acinetobacter baumannii*. Acinetobacter is quite hardy and can survive on moist or dry surfaces for days (it has also been seen with increased frequency in soldiers evacuated from Iraq during both the Gulf War and the current conflict). Burkholderia and melioidosis causing wound infection were also seen in several patients.

Respiratory infections complicating submersion and aspiration were also not uncommon, with unusual organisms such as aeromonas and pseudomonas not infrequently identified. A number of highly resistant pseudomonas, aeromonas, and stenotrophomonas spp. causing pulmonary infections were isolated. In addition, the usual respiratory nosocomial infections were encountered.

In addition to these, patients also carried home a number of interesting enteric pathogens, including shigella, salmonella, giardia, and amoeba.

A significant problem encountered was the lack of contact precautions during evacuation and transport; although Maegele et al learned to provide respiratory and contact isolation immediately upon arrival to subjects, until

culture results were available. The Tsunami victims sadly provided a crash course in microbiology, with a wide variety of respiratory, enteric, and endemic pathogens, but with a higher frequency of antibiotic resistance than anticipated. ■

Update on Tenofovir

Delaunay C, et al. *J Virol*. 2005;79: 9572-9578; Wirden M, et al. *J Virol*. 2005;76(3):297-301; Nevins AB, et al. *Antiviral Therapy*. 2005,10:S18.

EMERGENCE OF K65R DURING therapy: Triple nucleoside combinations have been discouraged, based on reports of high rates of early virologic failure, especially in patients receiving various combinations of abacavir, 3TC, ddI, and tenofovir. Such failure was often associated with the emergence of K65R and M184V/I mutations. Newer data suggests that the early emergence of K65R in patients receiving triple nucleoside/tide combinations may be more common than previously suspected.[1] A group of treatment-naïve patients received a combination of abacavir, 3TC, and tenofovir once daily for 12 weeks. Before initiation of treatment, bulk genotypic sequencing and a more sensitive clonal analysis of each patient showed only virus with a wild type RT sequence.

In 21 patients with detectable viral loads at 4 and/or 12 weeks of treatment, bulk sequencing analysis of the RT gene was performed. This demonstrated the presence of M184V/I in 12 of 19 patients (63%) and K65K/R in 2 patients (10.5%) at 4 weeks of therapy. At 12 weeks of therapy, M184V/I was detected in 18 of 20 patients (90%) and K65R in 13 patients (65%). However, using the more sensitive clonal analysis, the K65R mutation was found in 0.6 to 48% of 5 clones studied at week 4 and in 30% to 100% of clones examined at week 12. This finding suggests that the emergence of K65R may occur more frequently and more rapidly than previously suspected. The 2 mutations appeared to arise independently within separate clones.

In the second study above, Wirden and colleagues assessed the frequency of thymidine analog mutation (TAMs) before and after initiation of tenofovir.[2] None of the patients had K65R present at baseline. Following initiation of therapy, K65R developed in 19 of 96 patients (20%). In regression analysis, K65R occurred significantly more frequently in patients without pre-existing TAMs compared with those with TAMS, as well as in those treated only with triple nucleoside regimens. Five patients had emergence of K65R in conjunction with TAMs or L74V at the time of failure. Most of the mutational changes detected, occurred at codons 74, 75, 115, and 118,

Salvage therapy in those with K65R: The significance of the K65R reverse transcriptase (RT) mutation on virologic response in patients receiving salvage therapy has not been well-examined, especially in patients with additional resistance to other TAMs. In the abstract above from Stanford University, these authors identified 144 patients with K65R from a bank of archived data for 6147 HIV-infected patients in California. Only 39 of these had sufficient information available regarding their treatment history and, following a change in their regimen, at least one measurement of plasma viral load. Most of these 39 patients had been heavily pretreated, including prior use of (in descending order) 3TC (92%), ddI (72%), tenofovir (64%), and abacavir (46%); 49% had used both ddi and tenofovir in combination. Baseline RT mutations were detected in 34 of 39 (87%), including 44% who had at least one TAM and 13% who had ≥ 3 TAMs.

Of the 39 patients, 36 (92%) were switched to a protease-inhibitor containing regimen. Eleven patients received tenofovir, despite evidence of K65R in all. Compared with baseline, the median decrease in viral load was ~1.7 logs at 3 months and ~2 logs at 5 months of therapy. About one-third achieved plasma viral loads < 50 copies/mL. Thus, the presence of K65R did not appear to diminish short-term outcome in this group of heavily pre-treated patients who were predominately salvaged with a protease-inhibitor containing regimen. This data suggests that about one-third of patients with the K65R mutational change can be successfully virologically suppressed with a change in their regimen, despite a history of extensive pretreatment and frequent TAMs. Whether continued treatment with tenofovir in the presence of K65R is of value was not assessed in the study. ■

INFECTIOUS DISEASE ALERT®

A monthly update of developments in infectious disease, hospital epidemiology, microbiology, infection control, emporiatrics, and HIV treatment

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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.

Beta-Blockers May Be Useful for Noncardiac Surgery

High risk patients benefit from perioperative beta-blockers when undergoing major noncardiac surgery according to new study. Researchers from Tufts University reviewed the records of 782,969 patients in 2000 and 2001 at 329 hospitals throughout the United States. Patients were graded with the Revised Cardiac Risk Index (RCRI), which takes into account high-risk surgery, ischemic heart disease, cerebrovascular disease, renal insufficiency, and diabetes. The RCRI is graded on a 0-5 point scale, with 5 representing the highest risk. High risk surgery included all intrathoracic, intraperitoneal, and superinguinal vascular procedures. Patients with contraindications to beta blocker therapy were excluded. Over 660,000 patients had no contraindications to beta-blockers, and 120,338 patients received beta-blocker treatment during the first 2 hospital days. The relationship between perioperative beta-blocker treatment and the risk of death varied directly with cardiac risk. Patients with an RCRI of 0 or 1 were found to have no benefit from beta-blocker treatment, whereas for patients with an RCRI of 2, 3, or 4, or more the adjusted odds ratio for death in the hospital, were 0.88 (95% CI, 0.80, 0.80-0.98), 0.71 (95% CI, 0.63 - 0.80) and 0.58 (95% CI, 0.50-0.67), respectively. The authors conclude that perioperative beta-blocker therapy is associated with a reduced risk of in-hospital death among high-risk patients undergoing major noncardiac surgery. They also noted that there was no benefit for low risk patients (Lindenauer PK, et al. Perioperative Beta-Blocker Therapy and Mortality After Major Noncardiac Surgery. *N Engl J Med*. 2005;353:349-361). An accompanying editorial points out that perioperative beta-blocker therapy has been somewhat controversial because of conflicting data in recent years. The current study shows an apparent benefit in high-risk patients, but they also look forward to the results of 2 ongoing randomized trials that will help clarify the role of beta-blockers for low-risk and intermediate-risk patients (Poldermans D, et al. Beta-Blocker Therapy in Noncardiac Surgery. *N Engl J Med*. 2005;353:412-414).

Promising New Weight Loss Drug?

More data shows that topiramate (Topamax) is associated with weight loss and, in this latest study, may also lower blood pressure in obese, hypertensive patients. In a study from Norway, 531 obese patients with hypertension were randomized to placebo, topiramate 96 mg/day, or topiramate 192 mg/day. All patients received the same diet, exercise, and behavioral modification advice. Patients were followed for 28 weeks. Mean weight loss was 1.9% for placebo and 5.9% and 6.5% for the 96 mg and 192 mg doses, respectively ($P < 0.001$ for each compared with placebo). Diastolic blood pressure was reduced 2.1, 5.5, and 6.3 mm Hg, respectively ($P < 0.015$ vs placebo). Systolic blood pressure was reduced 4.9, 8.6, and 9.7 mm Hg, respectively (P = NS). Paresthesia occurred in 33% of the active treat-

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Treating Shift-Work Disorder

Modafinil (Provigil) may be of some value for people with excessive sleepiness associated with shift-work sleep disorder. Researchers from Harvard randomized 209 patients with shift-work sleep disorder to receive either 200 mg of modafinil or placebo before the start of each shift. Modafinil resulted in modest improvement in nighttime sleep latency (1.7 ± 0.4 vs 0.3 ± 0.3 minutes, respectively; $P = 0.002$). More patients also had improvement in their clinical symptoms based on multiple objective tests and patients diaries (74% vs 36%, respectively; $P < 0.001$). Patients taking modafinil also had reduction in frequency and duration of lapses in attention during nighttime testing of performance, and proportionally fewer patients reported having had accidents or near accidents while commuting home (both $P < 0.001$). These benefits, however, were mild, and patients treated with modafinil continued to have excessive sleepiness and impaired performance at night. The authors conclude that modafinil 200 mg at the beginning of a shift may improve shift-worker's performance as compared to placebo, although the benefit is modest (Czeisler CA, et al. Modafinil for Excessive Sleepiness Associated with Shift-Work Disorder. *N Engl J Med*. 2005;353:476-486). An accompanying editorial urges caution when interpreting these results and suggests "the current study does not adequately assess the clinical value of this particular drug in shift-work sleep disorder, nor does it justify writing more prescriptions for modafinil." The authors do note that up to 20% of workers in industrialized nations are shift-workers and calls for "further scientific studies to address in a cohesive manner the serious health and safety issues that surround us by virtue of us having become, to a large extent, a shift-working society" (Basner RC. Shift-Work Sleep Disorder--The Glass is More Than Half Empty. *N Engl J Med*. 2005;353:519-521).

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FDA Actions

The FDA has approved the first of the new class of drugs for the treatment of insomnia characterized by difficulty with sleep onset. Takeda Pharmaceutical's ramelteon (Rozerem) is a selective agonist at 2 melatonin receptors in suprachiasmatic nucleus, receptors that are thought to regulate circadian rhythm and sleepiness. Recently marketed sleeping medications target GABA receptors (ambien, lunesta) and, although these drugs are associated with less addiction and sleep latency then benzodiazepines, they are still designated as Schedule IV drugs. Ramelteon has shown no evidence of abuse or dependence potential and will, therefore, be marketed as a unscheduled drug. It is also approved for long-term use and has not been associated with memory impairment or impairment of motor ability. The most common adverse events associated with ramelteon were somnolence, fatigue and dizziness (> 2% over placebo).

Plan B, Barr Pharmaceutical's "morning-after pill" is being considered for over-the-counter approval by the FDA. The issue has become a political hot potato, and even briefly held up the Senate's confirmation of Lester Crawford, MD, as Commissioner of the FDA. It is expected that decision will be made by September. ■

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