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Conference Summaries: ICAAC 2001, IDSA 2001, and ASTMH

CONFERENCE COVERAGE

Editor's Note: *The following summaries represent a selection of papers from those presented at the meetings listed below. It is important to recognize that many of these summaries are extracted only from the published abstract, and it is possible that some of the material presented at the conferences may have differed. The abstracts can be found online at the URLs given. The 41st Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), Chicago, Ill, Dec. 16-19, 2001; http://www.icaac.org. The 39th Annual Meeting of the Infectious Diseases Society of America, San Francisco, Calif, Oct. 25-28, 2001; http://www.idsociety.org. The 50th Annual Meeting of the American Society of Tropical Medicine and Hygiene, Atlanta, Ga, Nov. 11-15, 2001; http://www.astmh.org. —* ***Stan Deresinski, MD, FACP***

Streptococcus pyogenes

Pediatric Onset Neuropsychiatric Disorder (PANDAS), consisting of obsessive compulsive, tic, or anxiety disorders, was associated with evidence of *S pyogenes* infection and appeared to respond to antibiotic therapy. (*ICAAC #1537.*)

In a study in Pittsburgh, 48% of Group A *Streptococcus pharyngeal* isolates in 2001 were resistant to erythromycin; none were resistant to clindamycin, consistent with efflux mediated resistance. (*ICAAC #LB-4.*) A marked increase in macrolide resistance among *S pyogenes* strains in Ontario, Canada, was temporarily associated with a similar contemporaneous increase in macrolide prescriptions. (*ICAAC #321.*)

A Belgian study found significant correlations for *S pyogenes* isolates with: 1) overall consumption of all macrolide antibiotics and erythromycin resistance; 2) consumption of azithromycin and erythromycin resistance; and 3) consumption of azithromycin and the presence of ermB. It was concluded that the data suggest that long-acting macrolides (presumably meaning azithromycin) exert a stronger selective pressure than others. (*ICAAC #1314.*)

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INSIDE

Bronchitis

Acute Bronchitis. Two hundred twenty adults with acute bronchitis were given dextromethorphan and an albuterol inhaler and were also randomized to receive either azithromycin or vitamin C (each given as 500 mg on day one followed by 250 mg daily for 4 additional days). Confirming previous results, antibiotic therapy was not associated with a clinically important difference in outcomes. (*ICAAC #905*.)

Acute Exacerbation of Chronic Bronchitis. Examination of 527 sputum specimens from 257 patients with acute exacerbation of chronic obstructive pulmonary disease found an "atypical" bacterial pathogen in only 2 specimens—both with *C pneumoniae*. (*ICAAC #906*.)

Telithromycin given for 5 days was as effective as comparator agents (amoxicillin/clavulanate and cefuroxime axetil) given for 10 days in the treatment of acute exacerbation of chronic bronchitis in randomized trials. (*ICAAC #909*.)

Community Acquired Pneumonia

Diagnosis. In nursing home patients being evaluated for possible pneumonia, an oxygen saturation < 94% (breathing ambient air) by pulse oximetry had a sensitivity of 80%, specificity of 91%, and positive predictive value of 95% for the diagnosis. In a follow-on study, using a decrease from their previous baseline of > 4% saturation as a threshold marker, these values were, respectively, 73%, 100%, and 100%. (*IDSA #31*.)

Severity Scoring. An analysis of the Pneumonia Severity Index (PSI) as a discriminator of the need for hospitalization in patients with community acquired pneumonia found that only 19 of 78 hospitalizations deemed inappropriate by PSI were, in fact, inappropriate when additional clinical criteria, such as the presence of nausea and vomiting, precluding the use of oral medications were considered. (*IDSA #3*.)

Antibiotic Therapy. In a retrospective cohort analysis, pre-admission antibiotic therapy did not affect length of stay, time to clinical stability, resource use, or mortality in patients with community acquired pneumonia. (*ICAAC #872*.)

A meta-analysis of 11 randomized trials published from 1966 through November 2000, involving 3348 patients in which a newer respiratory fluoroquinolone was compared to other commonly used oral antibiotics in the treatment of community acquired pneumonia found, among the evaluable patients, the summary odds ratio favoring fluoroquinolone therapy was 1.43 (95% CI, 1.13-1.80; $P = 0.003$). However, an analysis of the intention to treat populations (reported in 7 studies) found an odds ratio of only 1.20 (95% CI, 0.99-1.46; $P = 0.06$). (*ICAAC #1853*.)

Patients with community acquired pneumonia were randomized to receive either moxifloxacin or comparator therapy with amoxicillin 1 g t.i.d., clarithromycin, or both. The therapies were equally effective, but moxifloxacin was better tolerated. (*ICAAC #863*.)

Pooled data from randomized trials found that moxifloxacin therapy was effective in 22 of 23 patients infected with *M pneumoniae*, 13 of 14 with *C pneumoniae*, and 2 of 2 with *L pneumophila*. (*ICAAC #865*.)

Fifteen patients with *Legionella pneumonia* were treated with oral trovafloxacin, and 13 were given oral gemifloxacin with an overall clinical success rate of 93%. (*ICAAC #877*.)

A retrospective analysis found that fluoroquinolones (mostly levofloxacin) were as effective as erythromycin

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in the treatment of 53 patients with *Legionella pneumonia*, but the time to defervescence and length of hospital stay were shorter in fluoroquinolone recipients. (*ICAAC #878*.)

In vitro studies found that the rate of resistance mutation in a strain of *M pneumoniae* was 10^{-8} to 10^{-9} for levofloxacin and moxifloxacin and 10^{-6} to 10^{-7} for sparfloxacin. While levofloxacin and moxifloxacin appeared to primarily target DNA gyrase, sparfloxacin targets topoisomerase IV in this organism. (*ICAAC #144*.)

Cefpodoxime and cefditoren were equally effective in a randomized trial in the outpatient treatment of community acquired pneumonia. (*ICAAC #852*.)

Pooled analysis of 1373 patients with community acquired pneumonia treated with telithromycin in clinical trials found a clinical cure rate of 92.4%. (*IDSA #129*.) Telithromycin was effective in 100% of 57 patients with pneumococcal pneumonia, including 9 from whom pretreatment isolates were resistant to penicillin and/or erythromycin. (*ICAAC #857*.) Telithromycin was effective in the treatment of community acquired pneumonia due to *C pneumoniae* (clinical cure in 32 of 34), *M pneumoniae* (30 of 31), and *L pneumophila* (12 of 12). (*ICAAC #859*.)

Analysis of pooled data from 2 randomized trials found that IV moxifloxacin with switch to p.o. was as safe and effective as comparator agents in the treatment of patients with severe community acquired pneumonia. (*IDSA #124*.) Six hundred twenty-eight hospitalized patients with community acquired pneumonia were randomized to receive IV/PO moxifloxacin or IV/PO amoxicillin/clavulanate + clarithromycin. Moxifloxacin was superior to the comparator therapy with clinical cure rates of, respectively, 93% and 85% (95% CI for the difference, 2.9-13.2%). (*ICAAC #864*.)

Ertapenem and ceftriaxone (each 1 g IV q.24h.) were equally effective and safe in the treatment of "serious" community acquired pneumonia in two large multicenter randomized trials. (*ICAAC #855, IDSA #456*.) Analysis of pooled data from 3 randomized clinical trials found that meropenem was as safe and effective as comparator agents in the treatment of hospitalized patients with community acquired pneumonia. (*IDSA #125*.)

One hundred seventeen nonimmunocompromised patients with community acquired pneumonia admitted to the ICU were randomized (2:1) to receive levofloxacin 500 mg p.o. b.i.d. or IV ceftriaxone + IV or PO clarithromycin with later switch to oral antibiotics. The success rates were 90% in the p.o. levofloxacin recipients and 89% in the IV ceftriaxone recipients. (*ICAAC #870*.)

Treatment Failure. Sixty-four of 688 (9.3%) of cases of Gram-negative pneumonia were community acquired; 56% were due to *Pseudomonas*, 29% to *Klebsiella*, 8% to *Haemophilus,* and 6% to others. The 64 were elderly, had high severity scores, many had underlying lung disease, and 42% were admitted from a nursing home; mortality was 22%. Antibiotic resistant organisms caused almost two thirds of infections and initial empiric antibiotic therapy in these was inadequate in 63%, while this was true in only 17% of the remaining cases. (*IDSA #485*.)

Inadequate antibiotic therapy accounted for only 10 of 68 (15%) treatment failures in patients with community acquired pneumonia given empiric treatment in conformity with IDSA or ATS guidelines. The etiologies of pneumonia in these 10 included MRSA, *Pseudomonas* and anaerobes in one each, and either a fungus or *M tuberculosis* in the remainder. Among the 58 patients adequate antibiotic therapy, the most common reasons for clinical failure were sepsis, nonresolving pneumonia, and nosocomial infection. (*IDSA #2*.)

Streptococcus pneumoniae

Epidemiology. A CDC analysis led to estimates of 7200 to 1140 annual deaths in the United States from culture positive invasive pneumococcal disease. (*IDSA #875*.)

The prevalence of nasopharyngeal colonization with *S pneumoniae* in infants increased from 7% at age 2 months to 34% at 6 months in infants who did not receive the 7-valent pneumococcal conjugate vaccine; the comparable prevalences for vaccinated infants increased from 8.6% to 27.1%. The majority of isolates from both control and vaccinated children were vaccine-type. (*ICAAC #80*.)

A logistic regression analysis identified cigarette smoking as the only significant predictor of community acquired pneumonia due to *S pneumoniae*. (*IDSA #878*.)

Nasopharyngeal carriage of *S pneumoniae* was examined in children with nonresponsive acute otitis media treated with gatifloxacin. Although carriage was reduced during therapy, it resumed within days after the end of therapy and exceeded pretreatment levels by 2 to 3 weeks. Recolonization was mostly with new serotypes with decreased penicillin resistance. (*ICAAC #1825*.)

Vaccination. The state of Alaska recommends pneumococcal vaccination for high-risk persons aged 32 years and all adults older than 55 years of age every 6 years. A retrospective analysis of 180 persons with 3 or more pneumococcal vaccinations, 1 (0.6%) reported a

reaction (after third dose) compared with 5 (2.8%) in the comparison group (3 after first dose and 2 after the second dose). Thus revaccination on at least 2 occasions appears safe. (*ICAAC #95*.)

Concomitant administration of the 7-valent pneumococcal conjugate vaccine did not interfere with the antibody response to Hib-OMP vaccine. (*ICAAC #81*.) The 7-valent pneumococcal congugate vaccine maintained its immunogenicity when given concomitantly with a 5-component DtaP-IPV-Hib vaccine. (*ICAAC #85*.)

Diagnosis. The Murex Wellcogen rapid latex agglutination test, when performed on urine samples, was negative in 8 of 8 consecutive patients with culture demonstrated pneumococcal pneumonia. (*IDSA #195*.)

Antibiotic Resistance. Thirty-five percent of *S pneumoniae* isolates from 97 US community hospitals were nonsusceptible to penicillin and 32% were resistant to erythromycin. (*ICAAC #79*.) Penicillin nonsusceptibility in *S pneumoniae* appears to be decreasing in frequency in Canada. (*ICAAC #2102*.)

Analysis of 15,481 invasive *S pneumoniae* isolates in the United States found that the prevalence of macrolide resistance increased from 10.6% in 1995 to 20.4% in 1999. The median MIC of M phenotype isolates, which had increased in prevalence from 7.4% to 16.5%, escalated from 4 to 8 µg/mL. MLSB phenotype prevalence remained stable at 3-4%. Overall macrolide use increased 13%, but the use of "long-acting macrolide" (presumably meaning azithromycin) had increased 210%. (*IDSA #513*.) In Canada, the proportion of macrolide resistant *S pneumoniae* strains with mefA and ermB are approximately equal. (*ICAAC #1317*.)

Among 86 patients with macrolide-resistant pneumococcal bacteremia, 19 (22%) were receiving a macrolide at the time of their positive blood culture, while none (0%) of 141 matched controls with macrolide susceptible pneumococcal bacteremia were taking a macrolide at that time. Breakthrough bacteremia was seen with strains containing either *mef* or *erm* resistance genes. (*ICAAC #1850*.)

Carriage of an erythromycin-tetracycline resistance conjugative transposon was associated with reduced fitness in some, but not all strains of *S pneumoniae*. (*ICAAC #654*.)

Of 2421 isolates of *S pneumoniae* from across Canada, 6.1% were resistant to ciprofloxacin, 2.1% to levofloxacin, 1.8% to gatifloxacin, and 1% to moxifloxacin. (*ICAAC #730*.) Ten of 70 (14%) of Hong Kong *S pneumoniae* year 2000 isolates submitted to the PROTEKT study were fluoroquinolone resistant; all were susceptible to telithromycin, quinupristin/dalfopristin, and linezolid. Nine of the 10 were members of the 23F Spanish clone. (*ICAAC #703*.)

All 7 patients with pulmonary infection due to levofloxacin-resistant *S pneumoniae* had significant underlying pulmonary disease, and all had received prior antibiotic therapy (including levofloxacin in 5) for prior pulmonary infection. (*ICAAC #902*.)

Five hundred twenty-eight levofloxacin-susceptible strains of *S pneumoniae* from the TRUST4 study in 2000 were examined for fluoroquinolone resistance mutations. None were observed among the 270 isolates whose levofloxacin MIC was 0.5 µg/mL, while 15 (6%) of those with an MIC of 1 µg/mL had a *ParC* alteration and 3 (1.2%) had a *ParE* change. Ten of 14 (71%) of isolates with a levofloxacin MIC of 2 µg/mL had a *ParC* alteration; no *ParE* changes were detected. None of the 5268 strains had a *gyrA* alteration. Thus, 3.7% of levofloxacin susceptible pneumococci have a single mutation in the gene encoding topoisomerase IV. (*ICAAC #702*.)

The mutant prevention concentration (MPC) is defined as the lowest concentration of an antibiotic that prevents the emergence of resistant mutants from an initial inoculum of 10^{10} bacterial cells. Thus, theoretically, the lower the MPC (relative to clinically achievable serum and tissue concentrations), the less likely the antibiotic is to select out resistant mutants. The MPC90s of 160 isolates of *S pneumoniae* for gemifloxacin, moxifloxacin, gatifloxacin, and levofloxacin were, respectively, 0.5, 1.0, 2.0, and 8.0 µg/mL. (*ICAAC #732*.)

Rabbits with experimental pneumonia caused by strains of *S pneumoniae* with varying levofloxacin MICS were treated with levofloxacin in a dose designed to mimic a 500 mg b.i.d. dose in humans. In vivo mutations appeared when the AUC/MIC was below 26. A bacteriostatic effect was observed when the AUC/MIC was at least 34 and a 2-$\log_{10}$ CFU reduction was observed with an AUC/MIC of at least 43. Levofloxacin at this high dose was effective when the MIC was < 1.5 µg/mL, was ineffective when the MIC was > 2.0 µg/mL, and was associated with emergence of resistance when the MIC was > 1.75 µg/mL. (*ICAAC #2090*.)

Pharmacodynamic analysis using an in vitro system found that gatifloxacin suppressed selection of resistant mutants of *S pneumoniae* with an MIC of 0.25 µg/mL at inocula of both 106 and 108 at an AUC/MIC of > 50, a clinically achievable ratio. For a second pneumococcal isolate with an MIC of 1 µg/mL, however, AUC/MIC ratios of 200 and 500 were required. (*ICAAC #445*.)

Treatment. Retrospective analysis of 65 patients with community acquired pneumonia due to penicillin nonsusceptible *S pneumoniae* found that the cure rate was 80% in those treated with levofloxacin, 50% in

those treated with a cephalosporin, 38% in those given a cephalosporin plus a macrolide, 36% in those treated with penicillin, and 13% of those given a macrolide alone. (*ICAAC #2062*.)

Four of 4 pediatric patients with nonmeningeal invasive pneumococcal infection with bacteremia due to a cefotaxime-resistant strain with an MIC = 1 µg/mL were successfully treated with cefotaxime. Six adult patients with pneumonia caused by similar strains were also treated with cefotaxime; 2 died of infection—one after a single dose and one on day 8 of therapy. (*ICAAC #901*.)

The mortality rate among 13 patients with invasive nonmeningeal pneumococcal infection "resistant" to ceftriaxone (MIC = 2 µg/mL) who were treated with that antibiotic was 15%. (*ICAAC #903*.)

Haemophilus influenzae

The prevalence of *H influenzae* isolates with reduced susceptibility to ciprofloxacin (MIC > 0.12 µg/mL) increased from < 0.1% of isolates in previous years to 0.1-15% in 2000. Single mutations in *gyrA* or *parC* increased the ciprofloxacin MIC to 0.12-4 µg/mL, while the presence of mutations in both was associated with MICS > 16 µg/mL. (*ICAAC #LB-3*.)

Pertussis

Thirty-two percent of adults with a cough lasting more than 7 days (mean duration, 20 days) had evidence of pertussis. (*ICAAC #1542*.) The diagnosis of pertussis is, however, often problematic. In one large experience, outbreaks of cough illness were associated with apparently falsely positive PCR tests for *B pertussis*, resulting in resource misallocation. (*IDSA #104*.)

Revaccination, using the acellular pertussis vaccine, may prove to be a valuable tool in reducing the incidence of pertussis in adults. In a large national randomized trial, administration of acellular pertussis vaccine to adults and adolescents was associated with a protective efficacy of 77% (95% CI, 9-98%; $P = 0.07$). (*ICAAC #1291*.)

Diphtheria

An invasive clone of nontoxigenic *C diphtheriae* caused bacteremia in a number of the Vancouver, Canada, downtown homeless population. (*ICAAC #2282*.)

An outbreak of diphtheria occurred in a group of military trainees in Latvia despite a high level of prior vaccination. (*ICAAC #2283*.)

Skin and Skin Structure Infections

Necrotizing Fasciitis. Two patients with necrotizing fasciitis after intramuscular administration of medication were described. The authors suggest that MRI be performed to evaluate patients with pain out of proportion to clinical findings at an IM injections site. (*IDSA #178*.)

A cluster of cases of necrotizing fasciitis due to *C sordelli* occurred among black tar heroin users in Ventura County, California. (*IDSA #110*.) A patient with rheumatoid arthritis receiving etanercept developed necrotizing fasciitis due to *S pneumoniae*. (*IDSA #137*.)

Treatment. Ertapenem 1 g q.24h. and piperacillin/tazobactam 3.375 q q.6h. were equally effective in the treatment of complicated skin and skin structure infections in a randomized trial. (*ICAAC #1483, IDSA #111*.)

Staphylococcus

Colonization. There was a high degree of concordance in *S aureus* nasal carriage among household partners in an elderly population. (*ICAAC #1216*.) Persistent carriage was not a risk factor for mortality. (*ICAAC #1217*.)

Prospective screening found that 107 of 208 (51%) ICU and liver transplant patients were never colonized with *S aureus*, 21% were nasal carriers alone, 3% were rectal carriers only, and 24% had both nasal and rectal carriage. *S aureus* infection occurred in 3.7% of the noncarriers, 18.2% of those with only nasal carriage, none of the 7 with only rectal carriage, and in 40% of those with both nasal and rectal carriage. Rectal carriage (with or without nasal carriage), APACHE II score, and length-of-hospital stay were independent predictors of *S aureus* infection. (*ICAAC #2054*.)

MRSA. Three dogs and a horse, the owners of each of which had had recent contact with health care facilities, had MRSA infections with strains indistinguishable from the major clones affecting humans in Ontario, Canada. (*ICAAC #307*.)

An outbreak of community acquired MRSA in Alaska natives was associated with prior receipt of antibiotic therapy and with sauna use. (*IDSA #16*.) Sixteen of 1761 (0.9%) residents of 12 Alaska native villages had nasal colonization with MRSA, with clustering in 4 of the villages and with 94% of carriers residing in villages were steam bathing is common. MRSA carriage was associated with an increased risk of infectious skin diseases. (*ICAAC #310*.)

Two genotypes accounted for 78% of 97 MRSA iso-

lates recovered from outpatients attending a Wound Clinic in San Francisco, suggesting epidemiological association between many cases. (*ICAAC #306.*)

S aureus, *E coli,* and coagulase-negative staphylococci together accounted for 55% of 28,468 SENTRY Program bacterial blood stream isolates obtained during the 4 years ending December 31, 2000. The proportion due to *S aureus* increased from 22.9% to 27.9% and the proportion that were oxacillin-resistant increased from 21.8% to 33.2%. (*ICAAC #78*.) Thirty-nine percent of *S aureus* blood stream isolates from 97 US community hospitals were methicillin resistant. (*ICAAC #79.*)

A retrospective analysis found no difference in mortality in patients with MSSA or MRSA bacteremia and, among the 104 patients with MRSA, initial treatment with ineffective antibiotics did not significantly adversely affect outcome. (*ICAAC #UL04*.) In contrast, a prospective cohort study found that compared to MSSA, MRSA surgical site infection was associated with greater mortality, hospital charges, and number of hospital days after infection. (*ICAAC #2056*.) A retrospective cohort analysis found that MRSA bacteremia was associated with a significantly greater length of stay and costs when compared to MSSA bacteremia. (*ICAAC #1221*.)

A health care worker found to be colonized with MRSA during a hospital outbreak of infection with this organism and for whom repeated efforts of decolonization failed, was subsequently successfully colonized with MSSA. Replacement of the MRSA was associated with no further relapse of MRSA-related hospitalization. (*ICAAC #2057*.)

The most important risk factor for the development of MRSA bacteremia in a trauma center was having received > 48 hours of antibiotic therapy with activity against MSSA within the previous 30 days. (*ICAAC #1220*.) Prior levofloxacin use was among the factors associated with MRSA infection at one hospital. In vitro studies found that fluoroquinolone exposure increased the proportion of colonies of MRSA that grew on agar containing 128 µg/mL oxacillin; levofloxacin and ciprofloxacin were more potent in this regard than were gatifloxacin and moxifloxacin. (*ICAAC #1224*.)

Moxifloxacin and doxycycline were synergistic in vitro against 3 strains of MRSA. (*IDSA #578*.) Linezolid therapy failed to clear bacteremia in 2 patients with endocarditis due to MRSA. (*IDSA #533*.)

Glycopeptide Resistance. A case-control study involving 15 cases of infection with VISA or "SARV" (*S aureus* with reduced susceptibility to vancomycin) reported to the CDC found that they were associated with high mortality and that the major risk factor for such infections was prolonged vancomycin use. (*ICAAC #1230*.)

Of 79 MRSA bloodstream isolates from 65 patients at one northeastern US hospital, 24 (30%) exhibited heterogeneously increased resistance to vancomycin. The presence of such strains did not appear to affect patient outcomes. (*ICAAC #319*.)

A survey of 242 strains of *S aureus* (36% MRSA) isolated at 105 French hospitals in 1 month found that 7 strains were heterogeneously resistant to teicoplanin but susceptible to vancomycin. Four of 12 MRSA clones prevalent in French hospitals had intermediate susceptibility to glycopeptides (GISA strains) and these were isolated in 7 hospitals from geographically distinct areas. (*ICAAC #315*.) A separate survey of 63 French hospitals identified GISA in 27 (29%). (*ICAAC #317*.) Sixty-eight of 400 (17%) strains of *S aureus* at 1 Spanish hospital grew in the presence of 4 µg/mL of vancomycin and 2 (0.5%of the total strains) of these were heterogeneous GISA strains. (*ICAAC #2059*.)

In vitro studies found that linezolid is bacteriostatic against VISA. Against gentamicin susceptible strains, lenzolid antagonized the aminoglycoside's bactericidal activity. The combination of linezolid and vancomycin was indifferent against VISA. (*ICAAC #1418*.)

Triclosan has reduced activity against some GISA strains. (*ICAAC #2268*.)

Bloodstream Infection and Endocarditis

Predictors of complications in 724 with *S aureus* bacteremia adults present at initial evaluation were the presence of clinically evident emboli, hematuria, anemia, a diastolic or new murmur, abnormal skin exam, prolonged symptom duration, the presence of an orthopedic prosthesis, and admission to a surgical service. Hospital-or health care-associated bacteremia was less likely to be complicated than was community acquired bacteremia. Additional risk factors, when variables present at days 2-4 were included in the model, were blood culture positivity at days 2-4, failure to remove an infected source, increasing number of positive blood cultures, and persistent fever at 72 hours. (*ICAAC #1218*.)

With a median follow-up of 605 days after the occurrence of bloodstream infection (total, 149), 2 of 192 (1%) prosthetic joints in 133 patients became infected. The pathogen in both cases was *S aureus*, with diagnosis of joint infection 1182 and 1726 days after bloodstream infection. The overall 5-year probability of late prosthetic joint infection after all bloodstream infection was 1.85%, while that after *S aureus* bacteremia was 16.7%. (*IDSA #236*.)

In a 6-hospital study of 505 patients with *S aureus* bacteremia, 64 (13%) had endocarditis, including 7 patients who developed endocarditis after the onset of bacteremia. Two of 12 (7%) patients with a prosthetic cardiac valve developed endocarditis after bacteremia. Risk factors for endocarditis included the presence of valvular heart disease, injection drug use, community acquisition of infection, unknown portal of entry, and being nonwhite. Because persistently positive blood cultures despite 3 days of antibiotic therapy was also a risk factor, the investigators recommend obtaining follow-up cultures on all patients at that time, regardless of echocardiographic findings, and that those with positive results may require "more potent antibiotic therapy." (*ICAAC #1341*.)

Of 111 patients with nosocomial *S aureus* bacteremia, 56 (50%) were documented to be IV catheter-related, 38% had a source of infection other than an IV catheter, and 12% had primary bacteremia. The frequency with which endocarditis was diagnosed in these groups was, respectively, 5.4% (3/56), 10% (4/42), and 15% (2/13). Endocarditis was diagnosed during the acute episode in all 5 who had catheter-related or primary bacteremia, 2 as the result of persistent fever and 3 because of metastatic foci. Of 45 survivors with initially uncomplicated catheter-related and primary bacteremia, all treated for 10-14 days and who were followed for at least 12 months, none developed evidence of endocarditis. (*ICAAC #1429*.)

Two hundred twenty-two patients with IV catheter-related staphylococcal bacteremia were randomized to treatment with either quinupristin/dalfopristin, nafcillin or vancomycin. A complete clinical response was achieved in 53% of streptogramin recipients and 64% of recipients of comparator therapy (P = 0.2). Adverse events occurred more frequently in the quinupristin/dalfopristin-treated patients (13.3% vs 4.6%; P = 0.02). (IDSA #15.)

Eradication of the focus of infection in patients with *S aureus* bacteremia was associated with reduced mortality. (*ICAAC #1484*.)

A case-control study found that a delay in initiation of appropriate antibiotic therapy in trauma patients with *S aureus* bacteremia was associated with a longer duration of bacteremia (4 vs 3 days), leukocytosis (16 vs 6 days), and hospitalization (32 vs 20 days). (*ICAAC #396*.) A retrospective study found evidence of a reduced risk of complications from IV catheter-related *S aureus* bacteremia if the treatment duration was at least 14 days. (*IDSA #81*.)

Prosthetic Joint Infection. Rifampin with either ciprofloxacin or ofloxacin were synergistic in an animal model of prosthetic joint infection due to MSSA. (*ICAAC #1146*.) High-level resistance to rifampin is associated with reduced replicative fitness in *S aureus*. (*ICAAC #653*.)

Fifteen patients with hip arthroplasty infections due to staphylococci susceptible to rifampin underwent open debridement and were treated with rifampin plus either levofloxacin (12 patients) or clindamycin (3 patients) for 3 months. All but 2 of the infections occurred within 2 months of arthroplasty. Only 1 patient (who had a late infection) failed therapy. (*ICAAC #1460*.)

Pneumonia. Six hundred twenty-three patients with ventilator-associated pneumonia were randomized to receive either linezolid or vancomycin, each with optional aztreonam; cure rates in the 2 arms were similar. For patients with *S aureus* isolated at baseline, cure rates were 53.8% for linezolid and 43.5% for vancomycin (P = NS). (*ICAAC #1469*.) ■

CME Questions

15. Which of the following is correct?

a. Macrolide resistance in *S pyogenes* has not yet been detected in the United States.
b. In a randomized trial, there was no benefit resulting from the addition of azithromycin to nonantibacterial therapy of acute bronchitis.
c. A large study of patients with acute exacerbations of chronic bronchitis found that almost half were due to *Chlamydia pneumoniae*.
d. In a randomized trial, orally administered levofloxacin was as effective as intravenously administered ceftriaxone plus clarithromycin in nonimmunocompromised patients with community acquired pneumonia admitted to an ICU.

16. Which of the following is correct?

a. Cigarette smoking is an important risk factor for the development of community acquired pneumonia due to *S pneumoniae*.
b. The prevalence of macrolide resistance among *S pneumoniae* isolates in the United States has decreased signficantly in recent years.
c. *S pneumoniae* resistant to fluoroquinolones have not been reported from either Canada or Hong Kong.
d. The higher the MPC, the less likely an antibiotic is to select resistant mutants.

In Future Issues:

Azithromycin

UPDATES

By Carol A. Kemper, MD, FACP

Can Primary Care MDs Manage TB?

Source: LoBue PA, et al. *Int J Tuberc Lung Dis*. 2001;5:933-938.

COMMUNITY PHYSICIANS ARE AT THE front lines in the battle against tuberculosis (TB). They are often the first to recognize (or not) cases of active TB, and often provide the initial diagnostic evaluation and management. In San Diego County, where 319 cases of active TB were diagnosed in 1997, two thirds (65%) of the cases were managed by community physicians. San Diego represents a county with a fairly high caseload of TB, ~12% of which was INH resistant and ~1% was multi-drug resistant at that time.

To investigate the knowledge and practices of clinicians in the community caring for patients with latent or active TB, researchers at UCSD and the San Diego County Public Health Department distributed a survey to each of 384 physicians who had reported at least one TB case to the PHD in the years 1995 to 1997. The survey addressed basic questions regarding the diagnosis and management of patients with latent or active TB. A total of 150 physicians (39%) responded. Of these, 77% had been trained in the United States; 38% were infectious disease or pulmonary medicine specialists, internists (47%), family practitioners (21%), pediatricians (14%), or other (11%). Their experience in the management of patients with TB during the previous 2 years varied from 0-5 patients (59%), 6-10 (24%), or 11 or more (17%).

When compared with current practice guidelines, the number of correct responses was pretty good at 83%, although the accuracy of the responses varied widely (51-94%) and there were some glaring deficiencies: 1) 22% of physicians believed that 3 negative AFB sputum smears excluded a diagnosis of pulmonary TB (one hopes they misread the question!). Sputum smears are able to detect only 50-60% of active TB cases; 2) 11% believed that a negative CXR ruled out a diagnosis of active pulmonary TB; 3) 24% failed to recognize the minimum duration of treatment for active TB (6 months); 4) 49% failed to recognize a positive TST in patients with an abnormal CXR consistent with active or healed TB (5 mm); 5) 36% failed to correctly identify a positive TST in a patient with close contact with an active TB case (5 mm). Specialists and physicians trained in the U.S., were more likely to indicate correct responses, as were physicians with a greater level of experience (3 or more cases per year). Although the number of physicians responding to the survey was low, suggesting the survey results may not be entirely representative of the larger treating community, it nevertheless points out the continuing need for provider education in the management of latent and active TB. It also provides continued justification for the ongoing public health management and physician supervision of all reported TB cases. Although this is a relatively labor intensive public health measure, the need continues to outweigh the cost. ■

SV-40 in Non-Hodgkins Lymphoma

Sources: Vilchez R, et al. *Lancet*. 2002;359:817-823; Shivapurkar N, et al. *Lancet*. 2002;359:851-852.

THE ROLE OF SIMIAN VIRUS 40 (SV-40) in the development of "soft cell" cancers, such as sarcomas, certain lung and brain cancers, and lymphoma has long been debated. While some evidence suggests that the incidence of these cancers is not increasing, other data suggest that non-Hodgkin's lymphomas (NHL) is on the increase, possibly the result of an ever-aging population. Between 1955 and 1963, the early polio vaccines were produced using green monkey kidney cells. As a result, some believe that these early batches of vaccine, which were administered to possibly as many as 30 million people, may have been contaminated with SV-40.

Polyomaviruses, such as SV-40, JC virus, and BK virus, are generally species-specific, although JC and BK virus are 70% homologous with SV-40 virus, and viruses antigenically similar to SV-40 have been found in people with progressive multifocal leukoencephalopathy (SV-40-like-PML viruses). These viruses may also have the potential to transmogrity normal cells into cells with malignant potential. For example, experiments in transgenic mice suggest that the gene responsible for a regulatory protein of JC virus replication, called T-antigen, is oncogenic, and specific DNA sequences of JC virus T-antigen have been found in medulloblastoma cells in children (Kemper, CA. *Infectious Disease Alert*. 1999;17:136).

In these reports above, 2 independent laboratories detected a similar frequency of SV-40 antigen sequences in cells of NHL patients. In one study, specimens obtained from 68 patients with NHL were compared with tissues from hundreds of other tumors and 40 healthy "control" specimens. Using molecular techniques, DNA sequences corresponding to SV-40 T-antigen were found in 43% of NHL cells, compared with fewer than 10% of other tumor cells and none of the cells from healthy individuals. The other study found that 42% of cells from 150 NHL tumors tested positive compared with 186 negative nonmalignant control specimens. Sequences of other polyoma viruses were not detected. While no data regarding polio vaccine history for these viral "footprints" in human malignant cells will continue to be debated. ■

PHARMACOLOGY WATCH

GlaxoSmithKline Withdraws Lymerix: Company 'Cuts Losses' on Controversial Lyme Disease Vaccine

Citing poor sales, GlaxoSmithKline has announced that it is withdrawing Lymerix, the Lyme disease vaccine, from the market. The vaccine was the first, and only, Lyme disease vaccine on the market. Lymerix generated $40 million in sales in 1999, its first year on the market, but sales have fallen steadily since. The vaccine has also been plagued by controversy regarding side effects claimed by patients—side effects that seem to mimic Lyme disease and include arthralgias, fatigue, and neurocognitive symptoms. The FDA reviewed a study of 10,000 patients (5000 active vaccine, 5000 placebo) and found no increase in side effects with the vaccine. But because of continued complaints by consumers, the Centers for Disease Control (CDC) independently reviewed more than 900 reported side effects. In a report issued in January, the CDC declared that the vaccine was not associated with unexpected events. Despite the report and statistics that show Lyme disease cases reaching record highs, Glaxo has decided to cut their losses and is pulling the vaccine from the market.

Measles Vaccine Weathers Storm in Europe

An outbreak of more than 600 cases of measles in Germany has been reported in the last few weeks. Most cases have occurred in Bavaria, an area that is known as a hotbed of opposition to the MMR vaccine. The German pediatricians report that only 80% of infants in Bavaria received the first dose of MMR and only 60% of children received the second dose in 2000. European opposition MMR has centered in England and Germany after early research linked the vaccine to autism. A soon-to-be-published English study also suggests that the measles virus is present in children with ileocolonic lymphodular hyperplasia, a variant of inflammatory bowel disease, and speculates that the source of the virus may be MMR. News of the data, which will be published in the April issue of *Molecular Pathology*, was broadcast on the BBC. The lay press in England and other European countries has run many related stories, which have fed the fears of parents that the vaccine causes more harm than benefit. This is complicated by the fact that hundreds of lawsuits are currently pending in England—lawsuits filed by parents who feel that their children have been harmed by the vaccine. Vaccine-phobia exists in the United States but is less pervasive, in part due to the work of the National Network for Immunization Information (NNII), which has helped disseminate useful information to parents and physicians regarding childhood immunizations. The organization has set up a new web site to provide an on-line clearinghouse for vaccine information. The web site, which is sponsored by several medical professional societies and has an impressive advisory board, can be found at www.immunizationinfo.org. The Network is a non-profit and receives no financial support from the pharmaceutical industry. The web site has just added the recommended 2002 schedule for childhood immunizations. Changes for this year include recommendations for routine use of hepatitis B vaccine for all infants before hospital discharge, a schedule for catch-up vac-

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cinations for children who are behind on routine immunizations, and recommendations for preadolescent assessment of the vaccine status. The site also offers a color-coded, easy-to-use schedule for all childhood immunizations.

Too Many Injections for Children?

The concern of most American parents regarding vaccines has more to do with the sheer volume of injections that children must endure. Current recommendations call for children to receive up to 20 shots before their second birthday. The antigen load from these vaccines has also led researchers to explore a possible link between vaccinations and the immune mediated diseases such as asthma and type I diabetes. The Institute of Medicine recently issued a report on this topic entitled "Immunization Safety Review: Multiple Immunizations and Immune Dysfunction." The report was issued by the Immunization Safety Review Committee of the Institute of Medicine, which was initially convened in 1991. The report found no relationship between immunizations and type I diabetes or an increased rate of various infections including pneumonia or meningitis. The evidence was inconclusive regarding a relationship between vaccines and asthma. Surprisingly, the report states that a child's exposure to vaccine antigens is actually lower in 2002 than it has been in the past. This is due in part to the removal of the smallpox vaccine in 1971 and an improvement in the pertussis vaccine, which reduced the number of potential antigens 1000-fold. The report can be accessed at www.iom.edu. Another excellent review on this subject was published in the January issue of *Pediatrics*. Entitled "Addressing Parents Concerns: Do Multiple Vaccines Overwhelmed or Weaken the Infant's Immune System?" (*Pediatrics*. 2002;109:124-129).

Cancer Vaccine Fast-Tracked by FDA

The US Food and Drug Administration has granted fast track status a novel cancer vaccine developed by Antigenics Inc. The vaccine is currently in phase III trials for the treatment of renal cell carcinoma. The fast track designation was awarded for the treatment of metastatic melanoma, which will begin phase III trials later this year. The drug, HSPPC-96 (trade name Oncophage) is a "personalized cancer vaccine." The process involves creating an antigenic "fingerprint" for each individual tumor, then designing a vaccine to sensitize the immune system to specific tumor antigens. The fast track designation is reserved for drugs to treat serious life-threatening conditions and for which there is no existing treatment. The designation virtually guarantees a priority review of the drug when phase III trials are completed.

Once Yearly Osteoporosis Treatments a Possibility

Women may soon be able to make a once yearly appointment to treat their osteoporosis. A recent study shows that an annual infusion of the bisphosphonate zoledronic acid is as effective as more frequent dosing for the treatment of osteoporosis. A yearly infusion of zoledronic acid also appears to be as effective as daily dosing of other bisphosphonates, such as alendronate or etidronate. The study, which was performed in Europe, New Zealand, and Canada, followed more than 350 postmenopausal women with low bone density. The women were randomized to placebo or intravenous zoledronic acid given in several dose regimens at 3-month intervals, 2 mg given every 6 months, or a single 4 mg dose administered once a year. At the end of 1 year, bone mineral density was assessed in the spine and the femoral neck. Increases in bone mineral density at both sites were found in all active medication groups and the increase was similar in all dosing schedules including the 4 mg once yearly group. The effect was also similar to published results with other oral bisphosphonates. The authors suggest that a once yearly infusion of zoledronic acid may eventually be a realistic alternative to oral bisphosphonates (and all their attendant side effects including esophagitis). This study is a phase II trial. (*N Engl J Med*. 2002;346:653-661). An FDA advisory board on oncologic drugs also recently recommended the approval of zoledronic acid for the treatment of bony metastases associated with a broad range of tumors including breast cancer in lung cancer. Novartis plans to market zoledronic acid under the trade name "Zometa."

Niacin and Statin Use Found to Raise HDL Cholesterol

Even low doses of niacin can effectively RAISE HDL cholesterol when used in conjunction with a statin, according to a recent study. Fifty patients who are stabilized on a statin were randomized to receive niacin 50 mg twice a day or placebo. The primary end points were change in HDL cholesterol and side effects such as flushing. The niacin patients had an increase in HDL cholesterol of 2.1 mg/dL, an increase that was statistically significant. Only 5 patients taking niacin noted flushing vs. 2 patients in the placebo group. There were no other significant side effects noted (*Am Heart J*. 2002;143:514-518). This study is important because traditional niacin therapy uses doses of 2000-3000 mg, doses that frequently result in intolerable side effects for many patients. Using low doses of niacin in conjunction with a statin safe and well-tolerated way to increase HDL cholesterol. ■