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CFS: Another Hypothesis Leads to a Dead End

ABSTRACT & COMMENTARY

Synopsis: *The mineralocorticoid, fludrocortisone, failed to improve the symptoms of chronic fatigue syndrome patients.*

Source: Rowe PC, et al. *JAMA.* 2001;285:52-59.

This study, a joint effort of rowe and associates at the Johns Hopkins Hospital and the National Institute of Allergy and Infectious Diseases at the National Institutes of Health, evaluated the potential effect of the mineralocorticoid, fludrocortisone (Florinef) in patients with chronic fatigue syndrome (CFS). Subjects were highly selected on the basis of a strict definition of CFS, and criteria that excluded those with other specified medical and psychiatric conditions or use of any medications that might interfere with tilt-table testing or other elements of the study. Tilt-table testing identified subjects with neurally mediated hypotension (NMH), a sustained 25-mm Hg reduction of systolic blood pressure from baseline supine readings when tilted to a 70º upright position for up to 45 minutes (stage 1 testing) or when similarly tilted following isoproterenol infusion (stage 2). Most patients had CFS for at least 3 years (mean duration, 6 and 6.9 years in the placebo and treated groups, respectively). Fifty subjects received oral fludrocortisone in doses escalating from 0.025 mg/d for the first week to 0.1 mg/d from weeks 3 through 9; an identical number received placebo. Liberal water consumption was encouraged, but no change in the subjects' salt intake was recommended.

Subjects' well being was frequently assessed throughout the 9-week treatment period and a 2-week follow-up phase using standardized self-rating measures, including the SF-36 survey, the Beck Depression Inventory, and the Wood Mental Fatigue Inventory, and a unidimensional global wellness scale that has been used by the investigators in other studies of CFS patients. All patients had NMH as defined above. Tilt-table testing was repeated in most subjects at completion of the treatment period.

Rowe et al found in an intention-to-treat analysis that neither

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wellness scores nor any other self-rating measure improved over the course of the study. Likewise, tilt-table responses were not affected by fludrocortisone treatment.

Significant adverse effects were not observed. Interestingly, when subjects were asked whether they thought they were receiving placebo or active drug, incorrect assessments were slightly more frequent than correct responses, testament to the effective blinding of the study.

COMMENT BY JERRY D. SMILACK, MD

NMH refers to a disorder of blood pressure regulation in which a significant decrease in systolic blood pressure occurs upon assuming an upright body position, after other causes of orthostatic hypotension (such as dehydration or other states of intravascular volume contraction, medication, etc) can be excluded. Several investigators[1,2] have observed NMH to be a frequent accompaniment of CFS, a disorder that affects large numbers of individuals.[3] Although its cause is unknown, CFS has been the focus of much research, and investigators have identified a variety of objective markers that might provide a clue to the etiology of this perplexing syndrome.[4]

The suspicion that an altered hypothalamic-pituitary-adrenal axis is fundamental to CFS has been suggested by research demonstrating abnormal serum or urine adrenal hormone concentrations in some patients, either spontaneously measured or determined after provocative testing. To test the hypothesis that this arm of the endocrine system may play a role in CFS, several studies have examined the effect of administration of adrenal hormone in such patients. Cleare and associates, for example, found that low-dose hydrocortisone treatment (5 or 10 mg daily) resulted in improved fatigue and disability scores but had a less impressive effect on clinicians' assessment of patients' global depression.[5] This study used a crossover design but involved a relatively small number of subjects, and entailed only a short course (28 days) of treatment. On the other hand, McKenzie and associates conducted a study using a higher dose of hydrocortisone (25-35 mg/d) and found measurable benefit to be minimal.[6] They cautioned that adrenal suppression, observed in one-third of hydrocortisone recipients, might outweigh any slight benefit.[7]

The present study by Rowe et al, as well as a crossover, placebo-controlled trial conducted in Minnesota a few years ago,[8] examined the use of mineralocorticoid therapy in patients with CFS. Neither study demonstrated a beneficial effect of fludrocortisone. Overall, symptoms failed to improve significantly, and there was no measurable improvement in a variety of performance indices. Rowe et al concluded that the role of NMH in CFS remains an open question, but they were unable to show that fludrocortisone could ameliorate subjective or objective measures of illness, or improve tilt-table performance, in patients with CFS. ❖

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EDITORIAL GROUP HEAD: Glen Harris.

MARKETING PRODUCT MANAGER: Schandale Kornegay.

MANAGING EDITOR: Robin Mason.

ASSISTANT MANAGING EDITOR: Neill Larmore.

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VRE and UTIs—Don't Forget Nitrofurantoin

ABSTRACT & COMMENTARY

Synopsis: *Nitrofurantoin still appears uniformly active against vancomycin-resistant enterococci in cystitis.*

Source: Zhanel GG, et al. *Antimicrob Agents Chemother.* 2001;45:324-326.

Zhanel and colleagues tested 300 strains of enterococci collected in an ongoing Canadian surveillance study and tested them for susceptibility to nitrofurantoin. These included 100 strains of vancomycin-susceptible *Enterococcus faecalis*, 100 strains of vancomycin-susceptible *E faecium*, 50 strains of vancomycin-resistant *E faecium*, 25 strains of vancomycin-susceptible *E gallinarum*, and 25 strains of vancomycin-resistant *E gallinarum*. All were from stool samples from different patients and carefully identified and confirmed to be enterococci.

The 300 isolates were tested using NCCLS criteria with a panel of antibiotics including ampicillin, streptomycin, teicoplanin, ciprofloxacin, quinupristin-dalfopristin, and nitrofurantoin. The vancomycin-susceptible *E faecium* strains were highly resistant to ampicillin and the aminoglycosides, but the *E faecalis* strains were susceptible. Both were usually resistant to ciprofloxacin and some were resistant to quinupristin-dalfopristin as well. Remarkably, all isolates were susceptible to nitrofurantoin with MICs less than 1:128.

COMMENT BY ALAN D. TICE, MD, FACP

Enterococci have gone from being commensal, colonizing bacteria of the upper intestinal tract to one of the most feared and resistant organisms humans are faced with. They have clearly increased associated mortality and morbidity in hospitals and oncology units. They were the first of the common Gram-positive pathogens to become resistant to essentially all antibiotics available for systemic infections. Fortunately, they are not as inherently virulent and toxic as many of the other Gram-positive bacteria and may lie dormant in a normal host unless disturbed by alterations in the local microflora or by tissue trauma. Unfortunately, the stimuli for growth and the opportunities to cause disease are frequent and becoming more so with increasing use of potent antibiotics and immunosuppressives as well as surgery.

In the relatively normal host, enterococci play little role in disease. The exceptions are endocarditis and the urinary tract where they find their way into the bladder and sometimes the prostate or a kidney when the opportunities arise with faulty collecting systems. They account for about 5% of the bacteria causing uncomplicated cystitis in women and were commonly treated with ampicillin until they took a quantum leap in antibiotic resistance mechanisms that now may include enzyme production, aminoglycoside resistance, and the presence of *Van A, B,* or *C* coding for vancomycin resistance. While many *E faecalis* strains remain susceptible to ampicillin, an increasing number are resistant to gentamicin at high levels. *E faecium* is less frequently encountered but much more likely to be associated with ampicillin, gentamicin, and vancomycin resistance. *E gallinarum* is even less frequently a pathogen but is "intrinsically resistant" to vancomycin along with *E cassiflavus*. They can carry the *VanC* gene for vancomycin resistance although many strains retain their susceptibility to gentamicin and even ampicillin. There are some reports of a small percentage of enterococci with resistance to nitrofurantoin in the literature but most laboratory employees I have spoken with have not seen a strain.[1]

How frequently enterococci cause significant disease and what percentage of them are vancomycin resistant is unknown. It is clear, however, that the frequency of vancomycin resistance varies geographically. A recent report suggests half of enterococci isolated from patients in Santa Monica, Calif, are resistant to vancomycin.[2]

Nitrofurantoin offers an unusual opportunity to fight a new super bug with an old, cheap, and effective agent—almost a David and Goliath situation. Unfortunately, the circumstances for success are limited to infection of the urinary tract and, then, even further to the bladder. There are, nevertheless, reasons to keep the sling shot in your pocket and be ready to use it when a possible enterococci UTI appears in your office.

Exactly why nitrofurantoin has not fallen to the resistance mechanisms of enterococci after more than 20 years is unknown. It is a cousin of both furzolidone and fusidic acid, which is used for resistant Gram-positive infections in some countries. Although its mechanism of action remains unclear, it appears to act in the nucleic acid replication process. That is thought to be why it is antagonistic with the quinolones. Its resistance could also be related to its limited use in humans and possibly animal feed as well.

Although nitrofurantoin has a long and successful career in UTIs, there are a number of limitations and cautions in regard to its use. It does not reach effective concentrations other than in the urine so it should not be used for systemic infections and is of doubtful value in

even kidney and prostate disease. It may be used in pregnancy but not during the third trimester as delivery may expose the immature renal system of the fetus to an agent it cannot metabolize. Although it is assumed that in vitro activity correlates with in vivo success with nitrofurantoin for VRE UTIs, the studies have not been done to prove it with actual clinical trials.

Nitrofurantoin also has side effects, some of which can be severe. Gastrointestinal upset and headache are not unusual. It may cause a hemolytic anemia—especially with G6PD deficiency. It may also cause a neuropathy, leukopenia, hepatitis, and, at times, an unusual but classic pneumonitis that may be life threatening and associated with fever and often eosinophilia.

For uncomplicated cystitis, it should be given for 7 instead of 3 days to avoid relapses and to be sure of eradication. It may also be used for prophylaxis or, perhaps, suppression of UTIs, but the likelihood of adverse effects such as the pulmonary syndrome increases with time.

While nitrofurantoin will remain a mainstay for the therapy of cystitis, it may be worth considering alternatives, especially with increasing resistance of the Gram-positive organisms such as the enterococci. As mentioned, some of even the VRE may remain susceptible to ampicillin. Cipro may also be active despite susceptibility testing. Linezolid may also be considered and is now FDA approved for therapy. Intravenous therapy with quinupristin-dalfopristin is an added consideration for recalcitrant or systemic infections due to susceptible *E faecium*. ❖

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Antiseptics and Antibiotic Resistance

ABSTRACT & COMMENTARY

Synopsis: *The commonly used antiseptic, triclosan, may select for antibiotic resistance in P aeruginosa.*

Source: Chuanchuen R, et al. *Antimicrob Agents Chemother.* 2001;45:428-432.

Chuanchuen and colleagues, using a series of defined *Pseudomonas aeruginosa* mutants, evaluated the possibility that triclosan, a widely used antiseptic, may select for resistance to clinically useful antibiotics. A major mechanism of antibiotic resistance in this organism is the result of overexpression of efflux pumps. In vitro studies demonstrated that triclosan was a substrate for all 3 tripartite efflux pumps studied—MexAB-OprM, MexCD-OprJ, and MexEF-OprN. Triclosan resistance, which was selected at a frequency of 10^{-6}, was associated with a multidrug resistant phenotype and with a 94-fold increase in ciprofloxacin MIC. This resistance was associated with overexpression of the MexCD-OprJ efflux system resulting from a mutation in the nfxB regulatory gene.

COMMENT BY STAN DERESINSKI, MD, FACP

Triclosan is a 2-hydroxyphenylether antiseptic that is present in a wide variety of lotions, hand soaps, oral rinses, and toothpastes. It has even been incorporated into plastics and fabrics. Triclosan is more effective than chlorhexidine in reducing MRSA hand colonization, although the latter is more effective with regard to Gram-negative colonization.[1] The antibacterial activity of triclosan is the consequence of inhibition of a key enzyme in bacterial fatty acid synthesis, enoyl-acyl carrier protein (ACP) reductase (FabI). Resistance to triclosan has been associated with mutations in the gene encoding this enzyme.

Among the homologs of FabI normally susceptible to inhibition by triclosan is the enoyl-ACP reductase of *Plasmodium falciparum*, as well as mycobacterial InhA.[2] Mutations affecting this latter enzyme are associated with resistance to isoniazid in mycobacterial species.[3] This and other observations raised the possibility that triclosan may select for bacteria resistant to clinically useful antibiotics, a concern that was amplified by the finding that triclosan is a substrate of *E coli* multidrug efflux pumps.

Four multidrug resistance efflux systems (MexAB-OprM, MexCD-OprJ, MexEF-OprN, MexXY) have been characterized in *P aeruginosa*, and these account for most intrinsic antibiotic resistance in this organism. Chuanchuen et al have now demonstrated that triclosan is a substrate for at least 3 *P aeruginosa* efflux pumps and that triclosan resistance associated with overexpression of the MexCD-OprJ efflux system is selected in vitro at the very high rate of 10^{-6}. These triclosan-selected strains exhibit a multidrug resistant phenotype, including a 94-fold increase in MIC to ciprofloxacin. Overexpression of this efflux system was also associated with mutations in the nfxB regulatory gene.

In addition to its use in hospitals, triclosan has been incorporated into innumerable household and personal hygiene products. This has raised concern that the wide-

spread use of this and other antiseptics in everyday life may lead to acceleration of the development of resistance to clinically useful antibiotics. As an example, Chlorhexidine resistance in *S aureus* has been reported to be related to selection of staphylococci containing *qacA* genes, which encodes an efflux system, in multiresistance plasmids.[4]

Chuanchuen et al have demonstrated that antibiotic resistance may occur as the result of exposure to an antiseptic. This finding has real and urgent public health and policy implications. ❖

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Atovaquone Appears Effective and Well Tolerated in the Treatment of Babesiosis

CASE REPORT

Synopsis: *Studies in animals and humans suggest that atovaquone, administered in combination with a second agent, may be a safe and effective alternative to the standard clindamycin and with quinine for treatment of babesiosis.*

A 33-year-old previously healthy phd molecular biologist traveled to Madison, Wis, for a work-related function in late May 2000. Toward the end of her trip, she took a few days off to go hiking and camping about 1 hour north of the city. She returned to California on May 25 and within 8 days developed a high fever, headache, photophobia, neck stiffness, and swollen inguinal and axillary lymph nodes. She was seen in the emergency room, where she was found to be significantly orthostatic and was given parenteral fluids. Laboratory studies demonstrated mild leukopenia and elevations in hepatic transaminases. The presumed diagnosis was a "viral syndrome." During the next week, she continued to feel poorly with fevers to 103°F, and erythematous macules began to appear on her breasts, torso, and buttocks.

After surfing the internet, she approached her primary care physician (PCP) about the possibility of Lyme disease. Her PCP assured her that the rash did not resemble that of Lyme disease, but agreed to send an indirect immunofluorescence titer on June 8, which proved positive and was confirmed by Western blot. Before the results were available, however, the patient presented to an urgent care clinic on June 18 with an increasing number (~20) of pink and violaceous macules ranging in size from 1 to 6 cm, some with central clearing. She was treated with empiric doxycycline 100 mg twice daily for 3 weeks. Within 12 hours of the first dose, she experienced fever, rigors, and severe myalgias, which rapidly resolved.

After further surfing on the net, the patient approached her PCP regarding the possibility of co-infection with babesia. IFAs obtained on June 22 for *B microti* IgG and IgM were positive at 1:64 and 1:512. The patient was referred to an ID specialist for further evaluation. She was seen in consultation on July 18, at which time she was complaining of persistent fatigue and malaise, mild sweats, mild shortness of breath, a dry cough, and weight loss. The leukopenia had improved, the hepatic transaminases had normalized, a chest radiograph was unremarkable, and a direct smear for babesia was negative. But a PCR of whole blood for *B microti* obtained on August 8 was positive! The patient was reluctant to take quinine or clindamycin.

What Would You Do?

COMMENT BY CAROL A. KEMPER, MD, FACP

Based on the patient's desires for treatment, but also her valid concerns regarding drug toxicity (she was remarkably well informed), it was elected to treat her with a combination of quinine and azithromycin. Within 24 hours, she reported acute bilateral hearing loss, which quickly resolved with discontinuation of therapy. After further discussion, she decided to try atovaquone as a single agent 750 mg twice daily for 2 weeks. Two weeks after discontinuing treatment, a repeat PCR was negative, and the patient was feeling improved. Three months later, serologies for Lyme showed resolving infection, and babesia titers were less than 1:16.

Babesiosis is due to a malaria-like protozoan that parasitizes the erythrocytes of both wild and domesticated animals, birds, and humans.[1,2] More than 100 species of *Babesia* have been identified, although only the rodent strain, *B microti* (in the United States), and the cattle strains *B divergens* and *B bovis* (in Europe), are known to infect humans. Cases of babesiosis in humans were first recognized in 1960-1970 along the northeastern coast of the United States, in places like Nantucket Island, Mass, New York, and Rhode Island, but infec-

tions have also been reported in recent years in Virginia, Georgia, Wisconsin, Minnesota, California, Washington, and Mexico.

Because the arthropod vector for Lyme disease, *Ixodes dammini*, also serves as the vector for *B microti* in the United States, co-infection with *Borrelia burgdorferi* (as well as *Ehrlichia*) may occur, as was the case here. (Serologies for *Ehrlichia* were not obtained.)

Most cases of babesiosis are generally mild, and subclinical infection in endemic areas is probably not uncommon. Approximately 3-7% of individuals living in endemic areas along the northeastern seaboard have serological evidence of prior infection. While most cases of babesiosis are self-limited, the infection can present as a fulminant, malaria-like illness with hypotension and circulatory collapse, and may be fatal in up to 5% of clinically apparent cases. Clinically apparent infections are more likely in older persons, asplenic individuals, and individuals with underlying disease. HIV-infected persons have been reported to be at greater risk for more frequent and more severe infection.[3] However, 2 of the reported cases of babesiosis in HIV-infected individuals were also asplenic.[4,5]

Common laboratory findings include anemia, leukopenia, and abnormal hepatic transaminases. Hemolytic anemia has been reported, especially in splenectomized patients. With the exception of acute respiratory distress syndrome in patients with circulatory collapse,[2] respiratory disease is not reported, although this patient complained of persistent dry cough without evidence of radiographic disease that resolved with treatment. The incubation period is typically 1-3 weeks, but the onset of symptoms can be delayed for up to 6 weeks after infection. Based on the evidence, it is more likely this patient was suffering from acute babesiosis than Lyme disease at initial presentation.

The diagnosis can be made by examination of thin blood smears, indirect immunofluorescent antibody tests, or PCR. Serologies may be positive for as long as 1-6 years following acute infection and are generally not useful for tracking response to therapy. PCR-based assays specific for *B microtic* and *B divergens* are now available. A positive PCR for babesial DNA is believed to be consistent with ongoing replication and active infection, even in the absence of a positive smear, although the significance of this finding, especially in asymptomatic persons, is not known. Wild and domestic animals have been known to harbor babesial parasites for long periods of time, and a similar "chronic carrier state" may also exist in humans. Transmission of the organism through contaminated blood products from unsuspecting hosts is not infrequent in endemic areas, and persistent low-grade parasitemia has been reported in asymptomatic persons for months to years. Patients with immunodeficiency or HIV infection may be more likely to develop persistent parasitemia.

Whether patients who are asymptomatic, but with evidence of persistent residual infection by PCR alone, should receive treatment is not known, as many of these patients should successfully clear their infection on their own. A combination of clindamycin plus quinine for 1 week has been recommended in patients with acute infection, especially those with severe disease, although this regimen is poorly tolerated. Exchange transfusions have been used in life-threatening cases.

Recent animal data suggest that atovaquone has significant activity against *Babesia*, although it may not be sufficiently active as a single agent to eradicate infection. Atovaquone successfully suppressed *B divergens* infection in gerbils with as little as 1.0 mg/kg, with increasing effectiveness in dosages up to 10 mg/kg.[6] However, 10 days of treatment in a second study, even at higher dosages, failed to sterilize animals.[7] A combination of atovaquone and clindamycin was more effective at suppressing parasitemia but also failed to eradicate infection. Clindamycin and quinine were less effective than atovaquone alone when administered to hamsters before the animals were inoculated.[8]

Studies in cats experimentally infected with *Babesia felis* suggest that primaquine, as well as a combination of rifampicin and sulfadiazine-trionethoprim, may also be effective in suppressing infection, although buparvaquone, enrofloxacin, and danofloxacin had no significant effect.[9]

The emergence of resistance during treatment with atovaquone may also occur. Recrudescent parasitemia occurred in hamsters following the administration of atovaquone as a single agent.[10] When a blood specimen from hamsters with recrudescent parasitemia was inoculated into a subsequent series of animals, the second set of animals no longer responded to the administration of atovaquone. Better results were seen using a combination of atovaquone (100 mg/kg/d) plus azithromycin (150 mg/kg/d).

In humans, the combination of atovaquone and azithromycin appears to be similarly effective, but better tolerated, than the standard recommended regimen of quinine and clindamycin.[11] A total of 58 patients were randomized to receive either orally administered atovaquone (750 mg bid) plus azithromycin (500 mg on day 1 followed by 250 mg on subsequent days; n = 40), or quinine (650 mg tid) plus clindamycin (600 mg tid; n = 18) for 1 week. Fever resolved within 7-8 days

in both groups, and other symptoms had largely resolved within 3 months of treatment (65% of those receiving atovaquone plus azithromycin vs 73% of those receiving the alternate regimen). Three months post-therapy, smears and PCRs were negative in all subjects. Overall, the combination of atovaquone plus azithromycin was much better tolerated, resulting in side effects in only 15% of subjects vs. 72% of those receiving clindamycin plus quinine. The most common side effects to atovaquone plus azithromycin were diarrhea (8%), rash (8%) and vertigo (2%), compared with tinnitus (39%), diarrhea (33%), decreased hearing (28%), and vertigo (17%) in patients receiving clindamycin plus quinine.

Patients with life-threatening illness were excluded from this study, but successful treatment of a critically ill, splenectomized patient with azithromycin and atovaquone and exchange transfusion has been reported.[12]

Based on the improvement in the biologist's symptoms and laboratory studies before the initiation of treatment, her infection would have undoubtedly resolved without treatment. But her improvement with therapy suggests that she benefitted from effective suppression of her infection. Based on animal data, the administration of atovaquone as a single agent may be sufficient for milder cases or cases similar to ours (eg, smear-negative/PCR-positive). However, a combination of atovaquone, plus either azithromycin or quinine, should probably be used in cases with higher grades of parasitemia and more severe symptomatology. ❖

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CME Questions

15. Nitrofurantoin remains an effective antimicrobial for:

a. cystitis.
b. cystitis and prostatitis.
c. cystitis, prostatitis, and pylonephritis.
d. cystitis, prostatitis, pylonephritis, and endocarditis.
e. None of the above

16. What strains of enterococci are most likely to be susceptible to vancomycin?

a. *E gallinarum*
b. *E faecium*
c. *E faecalis*
d. *E casselflavus*

17. Which of the following is correct?

a. Intrinsic antibiotic resistance in *P aeruginosa* is most commonly the result of plasmid mediated beta-lactamase production.
b. The antiseptic, triclosan, is a substrate for several *P aeruginosa* efflux pumps.
c. The antibacterial activity of triclosan is the consequence of its ability to disrupt bacterial cell membranes by a direct, detergent-like effect.
d. Triclosan resistance in *P aeruginosa* is intrinsically linked with hypersusceptibility of this organism to ciprofloxacin.

18. Which of the following is correct?

a. In the United States, acquisition of babesiosis in humans is limited in geographic distribution to the northeastern coastal region.
b. Human babesiosis in the United States is transmitted by the bite of the tick, *Dermacentor andersonii*.
c. The tick vector of *Babesia* is also capable of transmitting *B burgdorferii* and the agent of human granulocyte ehrlichiosis.
d. Babesia infection in humans has a more than 90% mortality if untreated.

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In Future Issues:

Treatment of Severe Sepsis—
An Advance at Last!

UPDATES

By Carol A. Kemper, MD, FACP

Diagnosing Primary HIV

Source: Daar ES, et al. *Ann Intern Med.* 2001;134:25-29.

Daar and colleagues assessed the use of the p24 antigen and PCR HIV RNA test results in the diagnosis of acute primary HIV-1 infection, and whether any specific sign or symptom, or complex of symptoms, could be used to target screening for primary HIV. A total of 436 patients with signs and/or symptoms consistent with possible primary HIV infection were evaluated as part of 3 separate cohort studies performed between 1993 and 1999. The majority of the subjects were male (89%); 77% were homosexual, 18% were heterosexual, and 4% were intravenous drug users. Primary HIV was diagnosed in 54 patients (12.4%), all of whom had undetectable HIV antibody or an indeterminate Western blot, with documented seroconversion within 1 month. Eighteen percent were found to have chronic HIV infection with positive Western blot, and 69.5% had no evidence of HIV infection.

For the purposes of this study, Daar et al assumed that PCR for plasma HIV RNA had a sensitivity of 100% (the lower limit of detection ranged from 50 copies/mL to 500 copies/mL, depending on the cohort). Patients with negative HIV RNA on repeated testing and who did not seroconvert were considered to have initial false-positive HIV RNA results. The sensitivity and specificity of p24 antigen was 88.7% and 100%, respectively, whereas the specificity for HIV RNA was 97.4%. Five patients had detectable HIV RNA with high levels of HIV RNA but negative p24 antigens. Eight of 303 uninfected patients (2.6%) had false-positive HIV RNA tests (mean concentration 269; range, 52-1950 copies/mL).

Patients with primary HIV infection typically presented with symptoms common to most viral infections, including fever (87.5%), malaise (72.5%), myalgia (60%), rash (57.5%), headache (55%), night sweats (50%), and sore throat (42.5%). However, while patients with primary HIV were significantly more likely to report fever, myalgia, arthralgia, rash, or night sweats than persons without primary HIV ($P < .05$ in each case), no single sign or symptom, or complex of symptoms, was clinically predictive of acute HIV infection. Patients with primary HIV infection were more likely to be homosexual and to report a specific exposure to an HIV-infected person.

PCR assays for HIV RNA are more sensitive than those for p24 antigen in the diagnosis of acute HIV infection, but are associated with lower specificity and can lead to false-positive results, especially if the pretest probability is low (Kemper CA. *Infectious Disease Alert* 1999;18:80). False-positives are unlikely to occur at values less than 10,000 particles/mL of whole blood, and true-positive test results in primary HIV generally exceed 10,000 particles/mL. It is important to keep in mind that the interpretation of these test results depends on the clinical situation, the patient's risk factors, and confirmation of subsequent seroconversion. ■

Increasing Pneumococcal Resistance

Source: Whitney CG, et al. *N Engl J Med.* 2000;343:1917-1924.

Whitney and colleagues from the Active Bacterial Core Surveillance program of the Centers for Disease Control assessed 3475 isolates of *Streptococcus pneumoniae* obtained from patients with invasive infection in the United States during 1998. Overall, 24% of isolates were resistant to penicillin (PCN), up from 21% in 1995. During this 3-year period, overall resistance to cefotaxime increased from 10% to 14%, to erythromycin from 11% to 15%, and to trimethoprim-sulfamethoxazole from 25% to 29%. As has been previously reported, PCN-resistant isolates were more common in children younger than 5 years of age, and in whites compared with blacks. Georgia and Tennessee had the highest rates of PCN resistance (34%) compared with New York and California, which had the lowest (14.6%).

PCN-sensitive isolates generally remained sensitive to other antibacterial agents. In contrast, isolates with high-level PCN resistance were increasingly more likely to demonstrate high-level resistance to other agents (in descending order of frequency of resistance): cefuroxime (100%), trimethoprim-sulfamethoxazole (92%), erythromycin (61%), cefotaxime (42%), tetracycline (26%), chloramphenicol (14%), clindamycin (12%), and levofloxacin (0.7%).

These data don't look too different from earlier surveys—patterns of resistance are similar, but there's more of it. About one-third of all pneumococcal isolates are now resistant to at least 1 antimicrobial agent, and 14% are resistant to the 3 most heavily used agents in children for the treatment of otitis (amoxicillin, erythromycin, and trimethoprim-sulfamethoxazole). Resistance to clarithromycin and azithromycin, which was not specifically examined, can be extrapolated from these data.

Nearly 91% of the PCN-resistant isolates fell into 7 serotypes (6A, 6B, 9V, 14, 19A, 19F, and 23F), all of which should be covered by the 23-valent polysaccharide vaccine. However, clinicians should note that the new pediatric 7-valent conjugate vaccine would cover only 78% of the PCN-resistant isolates in this survey. Children who have received this vaccine are at significantly lower risk of invasive pneumococcal infection, but PCN-resistant invasive disease is still possible. ■