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Is it Full Speed Ahead with Postexposure Prophylaxis After Nonoccupational HIV Exposure?

ABSTRACT & COMMENTARY

Source: Lurie P, et al. Postexposure prophylaxis after nonoccupational HIV exposure. Clinical, ethical and policy considerations. *JAMA* 1998; 280:1769-1773.

This special communication to *JAMA* about postexposure prophylaxis (PEP) after nonoccupational exposure is bound to stir controversy. Although the title of the article implies that what will be presented are only considerations, this paper is a set of recommendations that, in fact, readers may find useful.

Lurie and colleagues begin with a review of PEP for occupational exposures. The risk for such exposures is fairly well known. After exposure to a known HIV-positive source involving body fluid, the risk of transmission is about 0.25%, but increases with exposure to large-bore needles or delivery of larger volumes of body fluid. Mucous membrane exposures are less risky (about 0.09%).

The CDC has produced its most recent guidelines for PEP in the occupational setting, which now include a more helpful algorithm to assist decision making.[1] In the hospital, the HIV status of the source patient is often known or can be obtained with rapid HIV testing that determines the HIV serostatus within several hours and at least helps modify the decision about duration of therapy.

The risk of seroconversion in nonoccupational exposures is generally not known. Nonetheless, several principles are key to understanding the approach to persons seeking PEP for their nonoccupational exposures. There are three important factors to consider: 1) frequency of exposure; 2) the probability that the source patient is HIV positive; and 3) the probability of transmitting HIV if the source patient is infected.

Exposure is considered to be either sporadic or continuing. Those exposures that are continuing (e.g., repeated sexual exposures), particularly if they occur more than once a month, require ongoing PEP.

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Regarding the serostatus of the source, only occasionally is that information available. Normally, the physician will have to estimate the likelihood that the source is infected from estimates of seroprevalence based on geographic location or databases gathered by the CDC in their National HIV Seroprevalence Surveys. The probability of transmission from an HIV-positive source for men who have single-encounter sex with men may approach 0.5%, which drops to 0.1% for exposures involving penile-vaginal intercourse. Other factors that may increase risk include a higher titre of virus, mucosal trauma, and concomitant genital tract infection.

Three case studies are presented for illustrative purposes. One involves an injection drug user who is HIV-negative and uses his own needles but has just shared a needle in New York City. It turns out the geographic location of the exposure would prompt PEP. The second case involves continuing exposure through sex with source status being unknown. Since there are few data from clinical trials, PEP cannot be recommended, but the patient should be referred for risk-reduction services. The last case involves sporadic exposure through sex for a college man who attends school in Nebraska. He and his regular partner were HIV-negative but last night's exposure involved another female student whose serostatus was unknown. Since the seroprevalence among college students is about 0.2%, the risk of transmission should be several fold lower than occupational mucous membrane exposure. The recommendation here is not to give PEP; there are, however, some contingencies. If the patient insists on PEP, he and his partner should be tested for HIV infection again and PEP stopped if both he and his partner are negative.

Other examples of sporadic heterosexual vaginal exposure produce more difficult decisions since they fall under medium probability. If the source is positive, PEP is appropriate. If the source is negative, the physician may have to weigh other factors such as the incidence of bleeding, trauma, concomitant genital infection, and geographic location of the source.

In instances of rape, the clinician may calculate that the risk is lower than in other incidences of sexual exposure but, because of psychological trauma and anxiety over pregnancy, PEP may be appropriate.

Lurie et al review the downside of PEP. We certainly do not want to send out a "double message" (on the one hand saying abstinence is best and safe sex is mandatory but if you slip up we will give you PEP). Lurie et al feel that this concept of "disinhibition" is not strong enough at this time to negate the value of PEP in the appropriate settings. Lurie et al emphasize that although some clinicians may be reluctant to give PEP for exposures that they deem irresponsible, clinicians still have an ethical duty to administer PEP when indicated. To quote Lurie et al, "Clinically, it is irrelevant whether the patient is an "innocent victim" or a "knowing participant." Their example of giving surgical care to an intoxicated traffic victim serves their argument.

Lurie et al also discuss the issues of timely access to PEP, difficulties with adherence and development of antiviral drug resistance, and cost considerations. Special sites for distribution of PEP may be necessary in some geographic locations. Adverse effects in my experience lead to a significant number of patients on PEP discontinuing their medication and adherence should be monitored in some way.

Regarding cost, Lurie et al calculate that the cost of $13,650 per year-of-life saved with PEP should make insurance companies willing to pay for PEP involving sporadic high-risk exposures. Consider some of their other cost estimates. For zidovudine (AZT) prophylaxis, the cost of preventing one HIV infection is $136,500. If a protease inhibitor is added to the regimen, the cost increases to $199,000. If the source patient's HIV status is unknown, the cost per year-of-life saved increases.

COMMENT BY JOSEPH F. JOHN, MD

JAMA has provided us with a true service in publish-

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ing this perspective. Lurie et al at UCSF have been involved with this issue for several years, their clinical setting being at one of the epicenters of the American HIV epidemic. Lurie et al have thrown out a challenge to clinicians who will be confronted with patients seeking PEP after nonoccupational exposures.

Table

Recommendations for Nonoccupational Postexposure Prophylaxis (PEP)

Exposure Frequency*	Probability of Transmission†		
	Low	Medium	High
Sporadic	Inform, but do not recommend	Consider	Recommend‡
Continuing	Inform but do not recommend; consider referral to risk reduction services	Inform but do not recommend; refer to risk reduction services	Inform but do not recommend; refer to risk reduction services

*Exposure frequency: *continuing*, more than once a month, and *sporadic*, less than once a month.

†Probability of transmission (the product of the probability the source is human immunodeficiency virus [HIV] positive and the probability of transmission for that act, if the source is HIV positive): *high*, unprotected anal intercourse or sharing of syringes with someone known to have HIV infection or of unknown HIV status but from a population with high HIV prevalence (about 30% or greater); *medium*, unprotected anal intercourse or sharing of syringes with someone of unknown HIV status from an intermediate-risk population (about 10-30% prevalence); unprotected penile-vaginal sex with known HIV-positive partner; and *low*, other risks such as oral sex, penile-vaginal sex, unprotected anal intercourse, or sharing of syringes with a partner of unknown serostatus in low-prevalence population.

‡Recommendations: *inform*, explain the concept of PEP, review benefits and risks, and explain that the likelihood of infection is low and that PEP is not advised; *consider*, inform patient and tailor decision to individual patient's desires and specific clinical situation; and *recommend*, inform patient and make clear that expected benefits outweigh the risks in his or her case and that PEP is, therefore, advisable.

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Exposures to blood and body fluids in the hospital have been a challenge to employee health services and infectious diseases sections across the country. Better guidelines and experience have allowed us to feel more comfortable about managing these types of exposures. Still, they require time, a great deal of organization, and full support from the hospital administration. After many years of overseeing services for PEP at our combined institutions, we succeed more times than not in successfully caring for healthcare workers with blood and body exposures.

PEP for nonoccupational exposures seems a horse of a different color, requiring a new mindset and new epidemiologic tools. Surely, those in charge of making decisions about PEP for occupational exposure will face some tough decisions. It will be interesting to see how sexually active populations gauge the value of PEP in the face of the degree of their risk taking.

The biggest public health risk in applying widespread PEP for nonoccupational exposures is probably the spread of resistant HIV. Although there is now documentation of transmission of resistant virus, it is not known if a short duration of exposure such as that with PEP can select a resistant quasispecies of HIV. Lurie et al make no definitive statements that PEP should in fact be HAART, but it would certainly be hard to offer patients less. The pressure on the clinician in such situations probably precludes any regimen other than HAART. One advantage of HAART is the likelihood that the combination would eradicate what should be a small inoculum of virus, thus, further limiting the emergence of resistant HIV.

It will be interesting to watch the evolution of these recommendations. At an earlier time when we had only reverse transcriptase inhibitors to offer healthcare workers with occupational exposure, few were eager to take PEP. Now that we have better scientific estimates of risk after exposure and much better antiretroviral regimens, clinicians will face patients that desire or even demand PEP. Physicians will need to weigh many ethical, social, and virologic variables in what may become a common outpatient dilemma.

Implementation of such a program has already been reported by the group from the Department of Public Health in San Francisco at the 1998 12th World AIDS Conference in Geneva. That health department became the first to offer medication, in-depth counseling, and HIV antibody testing to individuals who experienced non-occupational exposure via sexual exposure or needle sharing.[2]

To quote the abstract of the article, "Initially, there was a vociferous negative response by community groups about societal disinhibition and the erosion of established prevention messages, contrasted with resistance by HIV activists to any exclusion criteria established by research protocols."[2] Yet, through vigorous radio and other media awareness programs, the project gradually met with more acceptance. The experience of this ongoing San Francisco experience should become increasingly valuable for other cities planning nonoccupational PEP.

We clinicians all should have a zero tolerance for HIV risk taking. Nevertheless, PEP for nonoccupational exposures is becoming a reality that will put new and unique pressures on HIV care givers. ❖

References

1. Public health service guidelines for the management of healthcare worker exposures to HIV and recommendations for postexposure prophylaxis. *MMWR Morb Mortal Wkly Rep* 1998;47[No.RR-7]:1-34.

2. Kegebein VR, et al. 12th World AIDS Conference, Geneva, June 28-July 3, 1998. Abstract 251.

What behavior is considered "continuing" when considering post-exposure prophylaxis (PEP) for nonoccupational exposures to HIV?

a. Any type of anal intercourse
b. Standard therapy for hemophilia
c. Exposure to a sex worker every Saturday night
d. Unprotected sex with a girlfriend or boyfriend once a month

Once-Daily Dosing of Gentamicin

ABSTRACT & COMMENTARY

Synopsis: *In yet another confirmatory study, once-daily dosing of gentamicin proved as effective as traditional three-times-a-day dosing, with no increase in toxicity.*

Source: Gilbert DN, et al. A randomized comparison of the safety and efficacy of once-daily gentamicin or thrice-daily gentamicin in combination with ticarcillin-clavulanate. *Am J Med* 1998;105:182-191.

Yet another study comparing once-daily with thrice-daily aminoglycoside has demonstrated comparable safety and possibly diminished renal toxicity. This report describes three groups of patients randomized to receive either ticarcillin-clavulanate (TC) alone; TC plus gentamicin, the latter administered every 8 hours; or TC plus gentamicin, with the total daily aminoglycoside dose delivered every 24 hours. Patients, all suspected to have serious gram-negative bacterial infection, were comparable in terms of underlying disease (approximately half had malignancies), severity of illness (approximately one-fifth were in critical care units), and frequency of immunosuppression (some 20% were neutropenic and another 20% had AIDS). Only patients with estimated creatinine clearance of 30 mL/min or greater were enrolled.

A broad cross-section of infections routinely encountered in tertiary medical centers was represented in study patients, including unspecified fever in neutropenic patients, lower respiratory tract infections, peritonitis, biliary tract and intraabdominal sepsis, pyelonephritis, and skin and soft tissue infections. Bacteremia was documented in 23% of the 175 evaluable patients.

This study was different from most others of this type in that Gilbert and colleagues endeavored into each of the gentamicin treatment groups to achieve a predefined target serum concentration of gentamicin and found it necessary to adjust the dose upward within the first 48 hours in a substantial number of patients—particularly those receiving once-daily dosing. Duration of therapy averaged seven days but extended to as many as 55 days in one patient.

The results: nearly 90% of patients were clinically cured and had the infecting microorganism eradicated at the end of therapy in each of the gentamicin-containing regimens. A lesser success rate was achieved in the TC group, but the difference was apparently not statistically significant. Seven percent nephrotoxicity and 4-6% ototoxicity was encountered equally in each of the gentamicin treatment groups, although there was a suggestion (based on the fact that post-treatment renal function was unchanged or actually improved over base line measurements more often in once-daily gentamicin recipients) that once-daily treatment might be less toxic than every-8-hour dosing.

COMMENT BY JERRY D. SMILACK, MD

According to one survey, there have now been at least 30 published comparative trials to determine the efficacy and safety of once-daily vs. thrice-daily aminoglycoside dosing, and at least eight meta-analyses have been generated. Essentially all have concluded that clinical and microbiologic efficacy is equivalent, and toxicity seems no greater (some studies have even suggested less toxicity) with once-daily dosing. The message has gotten across. Whereas some 19% of hospital pharmacies reported once-daily aminoglycoside dosing in their hospitals in 1995, a recent report from the Infectious Diseases Society of America Emerging Infections Network, largely composed of infectious diseases clinicians, indicated that 70% currently prescribe or recommend once-daily gentamicin dosing, and some 55% of patients receiving gentamicin do so as a once-daily medication. A somewhat lower estimate from the CDC indicates that 28% of all gentamicin administered in the United States is done so in a once-daily regimen.

In an editorial accompanying Gilbert et al's paper, Gerberding highlights possible advantages of once-daily dosing:[1] equivalent efficacy and toxicity, fewer intravascular line-related infections, opportunity for outpatient treatment, and diminished cost of therapy. She concludes that "extended-interval dosing is the preferred aminoglycoside treatment regimen" for serious gram-negative infection in most patients, even those with neutropenia or other types of severe immunocompromise, for whom an anti-pseudomonal β-lactam should also be used. She recommends, however, that traditional multiple-daily dosing is warranted in patients with severe renal impairment or in those

where pharmacokinetics (drug distribution or clearance) may be difficult to predict, such as ascites, extensive burns, or massive fluid replacement, or where once-daily dosing has not been studied, such as pregnancy and pediatrics. Usage in endocarditis is uncertain. She also points out that it is unclear whether extended-interval dosing in patients with mild renal insufficiency should use reduction in the total daily dosage or extension of the dosing interval.

An unanticipated adverse effect associated with once-daily gentamicin dosing has recently been reported by the CDC.[2] A number of patients developed shaking chills, fever, tachycardia, and/or hypotension shortly after an intravenous infusion of gentamicin. The clinical scenario strongly suggested endotoxemia, and in fact it was discovered that patients receiving gentamicin supplied by one particular manufacturer contained endotoxin at a level higher than that found with other manufacturers' gentamicin, but still within USP-allowed limits for endotoxin in antibiotic formulations. Administration of a large dose of gentamicin in a single infusion permitted delivery of an amount of endotoxin that could result in overt symptoms, whereas administering the traditional 1.5 mg/kg dose q 8 h would deliver an amount of endotoxin below the known threshold for clinically apparent reactions. ❖

References

1. Gerberding JL. Aminoglycoside dosing: Timing is of the essence. *Am J Med* 1998;105:256-258.
2. Endotoxin-like reactions associated with intravenous gentamicin. *MMWR Morb Mortal Wkly Rep* 1998;47: 877-880.

The Infected Prosthetic Joint: When to Take it Out

ABSTRACTS & COMMENTARY

Synopsis: *Prolonged administration of antibiotics may successfully suppress prosthetic joint infection in some patients.*

Sources: Segreti J, et al. Prolonged suppressive antibiotic therapy for infected orthopedic prosthesis. *Clin Infect Dis* 1998;27:711-713; Karchmer AW. Salvage of infected orthopedic devices. *Clin Infect Dis* 1998;27:714-716. Editorial.

Segreti and colleagues at rush medical college accumulated 18 cases of patients with prosthetic hip or knee infections who were treated with prolonged suppressive antibiotic therapy without joint removal. The patients either refused removal or were thought unable to tolerate surgery. All of them had initial surgical debridement and 6-8 weeks of intravenous antibiotic therapy before being put on an oral agent known to be active against the identified pathogen. *Staphylococcus aureus* was recovered in eight cases—two were resistant to methicillin. Coagulase-negative staphylococci were recovered in seven cases. The other three included group B streptococci, *Moraxella* species, and *Streptococcus pneumoniae*. The oral antimicrobial regimens varied considerably and were given for an average of 49 months.

Of the 18 cases, three patients clearly failed antibiotic suppression and had their joints removed. In four cases, the patient quit antibiotic therapy after taking it for at least a year. One of those promptly relapsed within a month of completing a 22-month course of dicloxacillin. Three of the four failures involved infections due to methicillin-sensitive *S. aureus*; each had been treated with dicloxacillin. In only one case was dicloxacillin successful. The two methicillin-resistant *S. aureus* strains were treated with minocycline and rifampin and did well.

There were complications related to prolonged antimicrobial therapy in 22% of the patients. Four patients had *Clostridium difficile* diarrhea and two patients developed a drug rash, but the antibiotics were continued without apparent further adverse effects.

In an accompanying editorial, Karchmer reviews an additional series of patients with prosthetic joint infections. From these reports, he tries to draw some conclusions about the possible value of antimicrobial suppression. Some factors that seem to relate to a good outcome include whether the implant is stable, whether the infection is recognized early, and whether debridement is promptly performed. Also important is the lack of loosening of the prosthesis.

COMMENT BY ALAN D. TICE, MD, FACP

The article by Segreti et al adds another small series to the sparse literature about suppressing or possibly even curing infections of prosthetic joints without removing the hardware. This series and review, however, does provide some insight. Stability of the joint and pain are important factors to consider. In reviewing the series and advice from textbooks, it appears that the longer the infection is present, the less likely a successful outcome. It also appears that *S. aureus* is more difficult to eradicate or suppress than coagulase-negative staphylococci and possibly some of the other organisms.

The criteria for diagnosis of prosthetic joint infection also raises some questions. The recovery of coagulase-

negative staphylococci may not necessarily represent an infection and may, instead, be the result of culture contamination. They are a frequent contaminant with cultures. Even when truly there, these organisms may attach to foreign material and set up a glycocalyx that allows them to live on the joint surface in relative harmony with the host.

It is interesting to note that the cases reported by Segreti et al were all treated with surgical debridement without removal of the prosthesis. How extensive this surgery should be and how important this is remains a question—particularly if there is no obvious necrotic material to serve as a further nidus of infection. The 6-8 week course of intravenous antibiotics raises another question. Is a prolonged course of IV therapy necessary if oral antibiotics are to be used for suppression? Would two weeks be enough?

It is also interesting that there was such a high failure rate with dicloxacillin against *S. aureus*. The minocycline/rifampin regimen seemed to be effective and even seemed to work against methicillin-resistant *S. aureus*. The recent reports about the value of a quinolone plus rifampin should be considered.[1] Rifampin is a zwitterion with both a lipid-soluble and a water-soluble end. Its lipid solubility gives it the ability to penetrate white blood cells and then go on to penetrate the phagocytic vacuoles where microorganisms may be hiding. Dicloxacillin does not have the capacity for intracellular killing that rifampin does but the quinolones do.

Another question is how long oral antibiotics need to be given for an infection that is at least suppressed. If patients can tolerate long-term antibiotic therapy, it is advised that oral antibiotics be given for life, but, in this series, three of the four that stopped antibiotics after a year had not relapsed during the more than three years they were followed afterward. Unfortunately, there are no good laboratory tests to give us insight.

When to treat people with infected joint prostheses with limited surgical debridement and antibiotics remains uncertain. The apparent cure rates of 80-85% with removal and reimplantation (either early or late) of the prosthetic joint are difficult to compare with the series in which the joint is left in place—which has a success rate of 30-60% in other series. It should also be considered that the hosts in this population might not be as healthy; hence, infection might be more difficult to eradicate even if the joint is removed.

Other factors to consider in regard to joint replacement in the face of infection should include the host, the organism, and the duration of infection as well as the tolerance of oral antibiotics. If a prolonged course of oral antibiotics is opted for, one that contains rifampin would seem most reasonable. ❖

Reference

1. Zimmerli W, et al. Foreign-body infection (FBI) study group. Role of rifampin for treatment of orthopedic implant-related staphylococcal infections. *JAMA* 1998; 279:1537-1541.

Using Albendazole to Treat Microsporidiosis in AIDS Patients

ABSTRACT & COMMENTARY

Synopsis: *Albendazole was effective in the treatment and secondary prophylaxis of intestinal infection due to E. intestinalis in patients with AIDS.*

Source: Molina JM, et al. Albendazole for treatment and prophylaxis of microsporidiosis due to *Encephalitozoon intestinalis* in patients with AIDS. *J Infect Dis* 1998; 177:1373-1377.

Encephalitozoon intestinalis (formerly *Septata intestinalis*) is a microsporidial species that is an opportunistic pathogen in patients with AIDS. Diverse clinical manifestations of this infection include chronic diarrhea and cachexia that can be associated with cholangitis, sinusitis, bronchitis, conjunctivitis, and interstitial nephritis. Molina and associates conducted this randomized study of albendazole for treatment and prophylaxis of *E. intestinalis* infections in two hospitals in France in conjunction with SmithKline Beecham Pharmaceuticals. Given the results of the first interim analysis, enrollment of additional patients into this study was discontinued.

This study is unique in that all eligible patients underwent upper gastroduodenal endoscopy with duodenal biopsy to confirm the infection and to identify by electron microscopy the species involved. PCR was used to specify *E. intestinalis*. Molina et al intended to study an initial group of 10 patients. Patients were recruited between September 1994 and November 1996. However, two patients were excluded because electron microscopy analysis of their duodenal biopsies and PCR results from stool and intestinal biopsies showed that they were not infected with *E. intestinalis* but with *Enterocytozoon bieneusi* and *Encephalitozoon hellem*. Therefore, there were eight patients for evaluation. Only one patient did not have *E. intestinalis* detected in their duodenal biopsy by electron microscopy. However, this patient had *E. intestinalis* DNA by PCR as well as para-

sitologic findings confirming *E. intestinalis* infection in stool, urine, and bile samples. Microspordial spores could be found in urine in seven of eight patients. One patient had concomitant cytomegalovirus duodenitis and *Clostridium difficile* in his stools.

All patients were homosexual men with a history of chronic intermittent diarrhea and CD4 counts below 55 cells/cubic mm. Four patients were randomized to receive albendazole and four to receive placebo for a 21-day course. Premature discontinuation of therapy occurred exclusively in the placebo group. Microspordial spores were always detected in follow-up stool and urine specimens from patients randomized to receive placebo with no change in the semi-quantitative number of spores. By contrast, clearance of microsporidial spores was observed in follow-up stool specimens from the four patients randomized to receive albendazole. Urine specimens from two of these four patients still yielded microsporidia although the spores appeared to be altered.

These four patients underwent a second duodenal endoscopy with biopsies that failed to yield microsporidia when examined by histopathology and electron microscopy in three of four patients. In the fourth patient, electron microscopy revealed only what seemed to be remnants of microsporidial spore. All patients randomized to receive albendazole gained weight during the three-week study (mean, 4.1 kg; range 2.0-7.5 kg). All patients in the albendazole group had formed stools at the end of the treatment compared with none in the placebo group. Also, decreases in alkaline phosphatase and creatinine levels were noted in the albendazole group associated with disappearance of leukocyturia.

In the next phase of the study, the four patients without cure completed a 21-day course of open-labelled albendazole and cleared *E. intestinalis* from follow-up stools and intestinal biopsies. Thus, the overall cure rate of the albendazole regimen in their study was 100% (8 out of 8; 95% confidence interval 0.64-1.0%). Urinalysis still yielded microsporidial spores in three of these patients at the end of the treatment.

The prophylaxis phase of the study randomized the eight patients to receive maintenance therapy with albendazole 400 mg twice daily or no treatment. During the study period, none of the three patients receiving maintenance therapy had a recurrence of *E. intestinalis* infection (mean follow-up 7.7 months; range 6-9). Microsporidial spores were no longer detected in the urine samples of these patients. Three relapses were recorded among the five patients receiving no prophylaxis. Two of the relapses occurred in patients with persistent asymptomatic shedding of microsporidial spores in urine. Death occurred in four patients during follow-up (in three receiving no prophylaxis and in one receiving albendazole). By log rank analysis, albendazole had no significant effect on mortality during follow-up. There were no serious adverse effects reported during the double-blind study related to albendazole. Adverse events reported included headache and gastrointestinal events that were not different from placebo.

COMMENT BY GEZA RUSZKA, MD

Even though the numbers are small, based on these studies, it appears that albendazole is safe and effective for treatment and long-term prophylaxis for *E. intestinalis* infection in AIDS patients. It also appears that albendazole is probably effective for *Encephalitozoon* species other than intestinalis so that the strict diagnostic criteria observed during this study may not be necessary for clinical treatment of patients. Persistent shedding of spores in the urine might be associated with relapse because two of the three relapses occurred among the three patients who had microspordial spores in the urine of two patients detected at randomization who received no treatment. The issue of urinary shedding requires further study.

In the useful chapter by Carolyn Peterson on microsporidiosis available on the Internet (http://hivinsite.ucsf.edu/akb/1997/06mispor/index.html), it is noted that albendazole is an inhibitor of tublin polymerization and has a chemical structure related to metronidazole. Nevertheless, albendazole has been associated with *C. difficile colitis* in an AIDS patient under treatment for microsporidiosis. Because severe pancytopenia has been associated with albendazole therapy for *Echinococcus* infection, WBC counts need to be monitored in HIV-positive persons treated with albendazole. *(Dr. Ruszka is Clinical Assistant Professor of Medicine, Robert Wood Johnson Medical School-UMDNJ, New Brunswick, NJ.)* ❖

CNS Involvement in Herpes Zoster

ABSTRACT & COMMENTARY

Synopsis: *CNS abnormalities are commonly present in patients with herpes zoster.*

Source: Haanpaa M, et al. CSF and MRI findings in patients with acute herpes zoster. *Neurology* 1998;51: 1405-1411.

Fifty immunocompetent patients, 22 men and 28 women, with acute herpes zoster but without clinically evident CNS complications including signs of meningeal irritation, encephalitis, or myelitis underwent CSF study (n = 46), MRI (n = 16), or both (n = 16) to correlate laboratory abnormalities with clinical findings and outcomes. CSF analysis included measurement of cell count, total protein, IgG index, oligoclonal banding (OCB), IgG and IgM anti-varicella zoster virus (VZV) antibodies, and PCR assay for VZV DNA. MR imaging comprised cranial (n = 12) or cervical studies (n = 4), for cranial or cervical VZV eruptions, respectively, but due to flow artifacts, thoracic and lumbar cord MRI scans were not performed. Statistical analysis included Fisher's exact test, log-linear modeling, and logistic regression.

CSF pleocytosis was present in 46% (21/46) overall, and was seen in the first sample in 17 of the 21 patients, was present in the first sample in seven of seven patients with HZ-related MR abnormalities but in only one of four patients with a normal MRI (P = 0.01). OCB was present in 9% (4/43), two of which had HZ-related MR findings. Approximately 25% each had elevated CSF protein, anti-VZV IgG antibodies, or VZV DNA, but this did not correlate with clinical outcome or MR abnormalities. IgG index was abnormal in only one of 42 patients. Overall, CSF analysis demonstrated at least one abnormality in 61% (28/46), and MRI findings attributable to HZV were seen in 56% (9/16). None of the MRI abnormalities were enhanced with gadolinium, implying only mild inflammation or necrosis unlikely to lead to permanent changes. Interestingly, five of nine patients with abnormal MR scans developed post-herpetic neuralgia (PHN) within three months. PHN affected none of seven with normal MR imaging. The numbers are too small to be predictive but if extended to larger studies, may influence the initiation of treatment for HZ and prevention of PHN.

COMMENT BY MICHAEL RUBIN, MD

This study confirms the high frequency of CNS involvement in patients with herpes Zoster. Of interest is the apparent association of MRI abnormalities with the development of the most frequent disabling complication of this infection, PHN. Pain control in PHN remains challenging. Standard therapy includes amitriptyline (AT) but lack of efficacy (up to 50%) and unpleasant side effects limit its usefulness (Watson CPN. *Neurology* 1995;45(suppl 8):58-60). In a double-blind, randomized cross-over trial of 31 patients suffering moderately severe PHN for at least half-a-day for three or more months, amitriptyline was compared to nortriptyline (NT), its major noradrenergic metabolite, for efficacy and side effect profile. Patients with cardiac disease, seizures, brain damage, alcoholism, and severe depression were excluded. Treatment for five weeks, with a two week wash-out period before cross-over to the other agent, was initiated at 10-20 mg and increased by 10 mg increments every 3-5 days. Primary outcome measures, taken weekly, included pain evaluation, pain relief, and sleep (all measured using a visual analogue score), depression (using the Beck Depression Inventory), side effects, disability, and overall satisfaction.

AT and NT equally controlled pain in about 50% showing no significant difference with respect to mood, disability, satisfaction, or use of concomitant analgesic medication. Mean dose was 58 mg and 75 mg for AT and NT, respectively, among responders, and 68 mg and 97 mg among non-responders. Side effects were more common in the AT group, including dry mouth, constipation, and drowsiness, but tolerability was comparable in both groups.

In a similarly designed double-blind crossover study of 38 PHN patients (including 16 from the AT trial!), controlled-release oxycodone, a semi-synthetic opioid analgesic, 10 mg (with titration up to a possible 30 mg) twice-a-day was found to be significantly more effective than placebo for relief of steady pain, paroxysmal brief pain, allodynia, disability, global effectiveness, and patient preference. Constipation, nausea, and sedation were more common with oxycodone but did not overly contribute to drug discontinuation. Oxycodone and tricyclic antidepresssants appear comparable in their analgesic efficacy for PHN. *(Dr. Rubin is Associate Professor of Clinical Neurology, New York Presbyterian Hospital-Cornell Campus, New York, NY.)* ❖

With Herpes zoster rash but in the absence of CNS disease, which of the following is correct?

a. CSF pleocytosis is present in about 10%.
b. Oligoclonal bands are present in about 25%.
c. Approximately 50% have elevated CSF protein.
d. Approximately 40% have elevated anti-VZV IgG antibodies.
e. MRI findings attributable to HZV may be seen in approximately 50-60%.

In Future Issues:

Summary of the 6th Conference on Retroviruses and Opportunistic Infections