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INSIDE

Spinal Epidural Abscess—Is Drainage Required?

ABSTRACT & COMMENTARY

Synopsis: *In this small, retrospective analysis, surgical drainage of epidural abscesses was not associated with improved outcomes, even in patients who presented with neurological deficits.*

Source: Siddiq F, et al. Medical vs Surgical Management of Spinal Epidural Abscess. *Arch Intern Med.* 2004;164:2409-2414.

Siddiq et al reviewed the management of 60 episodes of spinal epidural abscess in 57 patients seen over 14 years, ending in 2002. The lumbar or lumbosacral region was involved in 54%, the thoracic in 18%, and the cervical in 28%. The number of vertebral levels involved was 1-8, with more than 2 vertebral levels involved in 45% of patients.

Blood cultures were positive in 26 (46%) patients, and abscess cultures were positive in 36 (63%). *Staphylococcus aureus* was recovered from 34 patients (60%), coagulase negative staphylococci from 5 (9%), streptococci from 9 (16%), *Enterococcus faecalis* from 3 (5%), Actinomycetes from 4 (7%), and other organisms from 8 (18%).

All patients received antibiotic therapy. Surgical decompression was performed in the management of 28 (47%) of episodes, and CT-guided percutaneous needle aspiration in 7 (12%), while medical management alone was administered in 25 (42%) of episodes.

Neurologic impairment was present at presentation of approximately half of all episodes, and was marked in 11. Complete recovery was achieved in 43 (72%) episodes, while an additional 10 (17%) were left with only minimal residual weakness. Recovery rates were similar regardless of the management mode. Only neurologic impairment at presentation was associated with a poor outcome. Complete recovery was achieved in only 17 of 30 (57%), with impairment at the outset of therapy, compared with 93% in those without initial impairment. Even in those 3with neurological complications at presentation, there was no significant difference noted in outcomes

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when surgical and non-surgical management were compared.

COMMENT BY STAN DERESINSKI, MD, FACP

The management of spinal epidural abscess has evolved over the last 2 decades, with the most important change being the recognition that not all patients require surgery for a successful outcome. The most generally agreed upon approach has been to intervene surgically only in patients with a neurological deficit resulting from the infection. Thus, patients presenting with a deficit as the consequence of cord compression are referred for urgent decompression. Those without an initial deficit are examined carefully several times daily for evidence of its appearance, an event that triggers referral for a decompressive procedure. In any case, antibiotic therapy is prolonged, although the duration is somewhat arbitrary, since there is no good clinical evidence upon which to base a recommendation regarding duration. The necessary duration of therapy, however, is likely to be longer in cases in which osteomyelitis and/or diskitis are present than when they are absent.

The mode of decompression has also evolved with the recognition that many spinal epidural abscesses can be successfully drained using percutaneous CT-guided aspiration.[1] This procedure was, in fact, used successfully in 7 of 7 episodes in this series. When successful, this mode of decompression, as well as of specimen acquisition for microbiological studies, has an obvious advantage over surgical decompression.

Accepting the implications of the report by Siddiq and colleagues at face value would, however, indicate that the approach to management described above results in unnecessary surgery in many patients. Siddiq and colleagues conclude that surgery is not required in most instances, even in patients presenting with a neurological complication of the infection. On the other hand, clinical experience has led to observations of sometimes apparently dramatic results from decompression, including the resolution of tetraplegia in some patients with epidural abscess involving the cervical spine.[2] It must be recognized that not all spinal cord complications in patients with this problem are amenable to surgical intervention or to percutaneous aspiration, since myelopathy may result from compression and/or thrombosis of spinal vasculature in the absence of cord compression.[3]

The retrospective nature of this study, patient heterogeneity, and small sample size all contribute to a wariness concerning its conclusions. I continue to believe that patients who develop a neurological deficit as the result of cord compression should be considered candidates for decompression, especially if this can be achieved by percutaneous drainage. I also continue to believe that an important key to a successful outcome is early recognition of this infection, since delayed diagnosis is associated with increased risk of permanent neurological deficit.[4] ■

References

1. Lyu RK, et al. Spinal Epidural Abscess Successfully Treated With Percutaneous, Computed Tomography-Guided, Needle Aspiration and Parenteral Antibiotic Therapy: Case Report and Review of the Literature. *Neurosurgery.* 2002;51:509-512.
2. Young WF, et al. Reversal of Tetraplegia in Patients With Cervical Osteomyelitis—Epidural Abscess Using Anterior Debridement and Fusion. *Spinal Cord.* 2001; 39:538-540.
3. van de Warrenburg BP, et al. Myelopathy Due to Spinal Epidural Abscess Without Cord Compression: A

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Thomson American Health Consultants accepts pharmaceutical sponsorship of some programs but only in the form of unrestricted educational grants that must meet all ACCME and ANCC requirements.

Diagnostic Pitfall. *Clin Neuropathol*. 2004;23:102-106.
4. Davis DP, et al. The Clinical Presentation and Impact of Diagnostic Delays on Emergency Department Patients With Spinal Epidural Abscess. *J Emerg Med.* 2004;26:285-291.

PCR and the Diagnosis of Occult Bacterial Infection in Hip Prostheses

ABSTRACT & COMMENTARY

Synopsis: *Previous studies have suggested that aseptic loosing of joint prostheses may be caused by infection with non culturable bacteria. This study found that PCR testing of operative specimens for bacterial 16s RNA did not identify the presence of bacteria if adequate microbiologic processing of specimens was performed and was negative.*

Source: Ince A, et al. Is Aseptic Loosening of the Prosthetic Cup After Total Hip Replacement Due to Nonculturable Bacterial Pathogens With Low-Grade Infection? *Clin Infect Dis.* 2004;39:1599-1603.

INCE ET AL STUDIED 24 PATIENTS WITH HIP PROSTHESES undergoing surgery for loosening of the prosthetic cup. All patients underwent pre-operative joint aspiration. At operation, specimens were obtained from the neocapsule and synovium; they were sent for culture and for PCR to detect 16s ribosomal RNA. Nine patients undergoing primary hip arthoplasty served as controls. All cultures were processed according to a protocol, with incubation in brain-heart infusion broth and TVLS medium, as well as Columbia blood agar in 5% CO_2 and *Brucella agar* under anaerobic conditions. All case and control patients had negative cultures, except for 1 case patient who grew *Proprionobacterium acnes* in a single operative specimen. All PCR determinations were negative. Patients had slightly, but not statistically significant elevated sedimentation rates and C-reactive protein levels, as compared to controls. Ince and colleagues concluded that good microbiologic processing of specimens is adequate to exclude bacterial infection in loosened hip prostheses, and that PCR does not enhance diagnostic sensitivity for infection.

COMMENT BY ROBERT MUDER, MD

The diagnosis of prosthetic joint infection is often difficult. There is no universally accepted definition for the diagnosis of infection in the absence of microbiological proof. Clinical symptoms such as pain and instability do not differentiate infection from mechanical joint failure. Several of the most common bacterial pathogens causing prosthesis infection, *P. acnes* and coagulase-negative staphylococci, are common skin contaminants. There is debate about the utility of histologic criteria, such as polymorphonuclear leukocyte count in tissue, in the diagnosis of infection.

To complicate things further, several studies using a variety of techniques have suggested that routine culture may fail to detect infection as a result of bacteria residing in biofilm. For example, Mariani et al[1] reported that the culture had only an 18% sensitivity in detecting bacteria in patients undergoing hip arthroplasty, as compared with PCR.[1] Tunny et al[2] subjected femoral prostheses removed from patients for loosing to sonication, followed by PCR, and found evidence of *P. acnes* or staphylococci in 72%. Cultures were positive in only 4% of patients.

One potential reason for the discrepancy between the results of Ince and colleagues and those of prior investigators may be the extent of microbiologic processing of both pre-operative aspirates and operative specimens. Ince and colleagues used multiple media and prolonged incubation times. Thus, the pre-operative aspirate may have identified a high proportion of patients with true bacterial infection—infections that might have been otherwise missed. This is of potential importance, as bacteria causing prosthetic joint infections residing in a biofilm, are relatively inactive metabolically, and may not be well adapted to growth in liquid or solid media. Less meticulous processing may fail to identify them.

This study does not fully resolve the question of whether bacteria undetectable by culture are responsible for a significant number of cases of prosthetic joint failure. The data are sufficiently convincing that I would feel comfortable withholding antibiotic therapy from a patient with a loosened prosthetic joint if pre-operative and intra-operative cultures were negative, and the ESR and C-reactive protein were normal or minimally elevated. It should be noted, however, specimens should be processed according to the above protocol; less extensive processing may give a false sense of security. ■

References

1. Marinani BD, et al. The Coventry Award: Polymerase Chain Reaction Detection of Bacterial Infection in Total Knee Arthoplasty. *Clin Orthop.* 1996;331:11-22.

2. Tunney MM, et al. Improved Detection of Infection in Hip Replacements: A Currently Underestimated Problem. *J Bone Joint Surg Br.* 1998;80:3281-3320.

Congenital HHV6 and HHV7 Infections

ABSTRACT & COMMENTARY

Synopsis: *HHV6 DNA was detected in 57 of 5638 (1%) cord blood samples, while HHV7 DNA was detected in none of 2129 cord blood samples. Congenital HHV6 infections were clinically and virologically distinct from postnatal HHV6 infections.*

Source: Hall CB, et al. Congenital Infections With Human Herpesvirus 6 (HHV6) and Human Herpesvirus 7 (HHV7). *J Pediatr.* 2004;145:472-477.

USING NESTED PCR CAPABLE OF DETECTING < 10 genome copies in cord blood mononuclear cells, human herpesvirus 6 (HHV6) DNA was detected in 57 of 5638 (1%) cord blood samples, and human herpesvirus 7 (HHV7) DNA was detected in none of 2129 cord blood samples. Two-thirds (38) of the 57 congenital HHV6 infections were with variant B (HHV6B), and one-third (19) with variant A (HHV6A). HHV6 IgG antibody was present in the cord blood of all 57 infants with congenital infection, but the geometric mean antibody titer was significantly lower in these infants than in 57 matched infants without congenital HHV6 infection (8.79 vs 9.48 $\log_2$, $P = 0.03$). HHV7 IgG antibody was present in all of the cord bloods that were tested (> 6.32 $\log_2$). The replicative state of HHV6 could be determined by RT-PCR in 48 (16 HHV6A and 32 HHV6B) cord blood samples. Active viral replication was documented in 5 of 48 (10%) infants, all of which were infected with HHV6B.

Follow-up PCR of peripheral blood mononuclear cells within 2 years of birth (46 samples from 17 children) showed 42 (91%) with HHV6 DNA. By comparison, follow-up within 2 years of postnatal HHV6 infection acquired > 1 month of age (1919 samples from 1044 children) showed 1327 (69%) with HHV6 DNA ($P = 0.03$). Active viral replication, as documented by RT-PCR, over the subsequent 2 years was demonstrated in 2 of 22 (9%) samples from children with congenital infection and in 45 of 1323 (3.4%) samples from children with postnatal infection.

COMMENT BY HAL B. JENSON, MD, FAAP

This study confirms the congenital infection rate reported by previous smaller studies, and is the first to study congenital HHV7 infection. It is surprising that no congenital HHV7 infection was detected because of the ubiquitous prevalence of both viruses and their virological similarity. In fact, HHV7 is shed more frequently in saliva (> 95%) of healthy adults, and, unlike HHV6, in 10% of breast milk samples. The divergence in HHV6 and HHV7 congenital infections is intriguing, given the genetic similarities of these viruses to each other and to cytomegalovirus (CMV).

This study shows interesting differences between congenital and postnatal HHV6 infections. Almost all postnatal HHV6 infections are caused by HHV6B, whereas one-third of congenital infections in this study were HHV6A. Congenital HHV6 infection was associated with a significantly greater frequency of detection of virus in peripheral blood mononuclear cells and a higher rate of active replication during the subsequent 2 years than with postnatal infection. However, most infants with congenital HHV6 infection did not show active HHV6 replication, which is very different from the high rates of CMV replication and shedding among infants with congenital CMV infection. In contrast to primary HHV6 infection that is often symptomatic, resulting in roseola, congenital HHV6 infection is asymptomatic, which may reflect the presence of maternal antibody in all cases. Congenital CMV infection is also usually asymptomatic at birth (90-95%), although infected infants are at increased risk for hearing loss and developmental deficits. It is unknown if infants with congenital HHV6 infection are at similar risk but this will be an important question to answer. ■

Lymphogranuloma venereum Outbreak in Gay Men

ABSTRACT & COMMENTARY

Synopsis: *Health-care providers should be vigilant for LGV, especially among MSM exposed to persons from Europe, and be prepared to diagnose the disease and provide appropriate treatment to patients and their exposed sex partners.*

Source: Van de Larr, et al. *Lymphogranuloma venereum* Among Men Who Have Sex With Men—Netherlands, 2003-2004. *MMWR.* 2004;53(42):985-988.

VAN DE LAAR ET AL REPORT AN OUTBREAK OF *Lymphogranuloma venereum* (LGV) among 92 gay men in the Netherlands over a 17-month period.

(the Netherlands typically has fewer than 5 cases per year.) Only 1 patient had symptoms typically associated with LGV (inguinal lymphadenopathy and painless genital ulcer). All other patients had predominant gastrointestinal symptoms including bloody proctitis with purulent or mucous anal discharge and constipation.

Laboratory diagnosis in these well-studied cases included PCR amplification from rectal swab specimens, followed by restriction endonuclease analysis of the outer membrane protein A gene to determine genotype. Confirmed cases were defined as clinical symptoms (or contact with a case), positive PCR for *C. trachomatis*, and L1, L2, or L3 genotype confirmed by PCR. Probable cases met the first 2 criteria and had a positive serologic test for *C. trachomatis*. Possible cases met only the first criterion and had a positive serologic test.

COMMENT BY DEAN WINSLOW, MD, FACP

Since this *MMWR* report was issued at the end of October 2004, an alarming number of cases of LGV have been reported from cities in the United States, also predominantly in gay men. On December 22, San Francisco Department of Public Health reported 9 cases of LGV during the month of November (the first cases of LGV in San Francisco since 2001).[1]

Additional cases have recently been reported from France, Sweden, Atlanta, and Houston.[2] Any possible epidemiological link between these cases is unknown at this time.

LGV is caused by the L1, L2, or L3 strain of *C. trachomatis* (serovars A, B, Ba, and C produce trachoma and strains D-K cause the more commonly encountered oculogenital syndromes).[3] The organism generally gains entrance to the body across epithelial cells of genital or anorectal mucosa or abrasions in the skin, and is almost always sexually transmitted, but transmission by fomites, nonsexual contact, and laboratory exposure has been rarely reported. A generally painless ulcer at the site of inoculation is often observed early in the course of the disease, followed by painful regional lymphadenitis and often prominent constitutional symptoms. In heterosexual men, tender, generally unilateral lymphadenopathy is often observed and can be noted both above and below the inguinal ligament, resulting in a groove sign (the differential diagnosis includes secondary syphilis, cat scratch disease, and other causes of lymphadenitis). Suppuration may occur. In homosexual men who practice receptive anal intercourse (and occasionally in women after heterosexual exposure due to lymphatic spread from the cervix or posterior vaginal wall), prominent perirectal and pelvic lymphnode involvement is seen. Later in the course of the illness (often years after initial infection), rectal stricture or elephantiasis of the genitalia may occur. Hyperplasia of intestinal and perilymphatic tissue often results in proctocolitis. Later, perirectal abscess, other pelvic abscesses, rectovaginal, and anal fistulas may be seen. In these late stages, it may be difficult to detect *C. trachomatis*.

Various nucleic acid amplification tests for *C. trachomatis* LGV-associated strains have been studied in the investigational setting. Commercially available complement fixation and microimmunofluorescence tests for *C. trachomatis* antibodies are relatively sensitive and specific for diagnosis of LGV. If acute phase sera are drawn early in the course of infection, a 4-fold rise in titer is observed. However, if serologic testing is not performed until the third week of illness, a stable positive titer of ≥1:64 (CF) or 1:128 (MIF) is considered diagnostic (titers this high are rarely seen with infection, due to the more common oculogenital strains).

Whereas uncomplicated *C. trachomatis* infections with oculogenital syndromes can be successfully treated with either a 7-day course of doxycycline or a single dose of azithromycin, successful treatment of LGV requires a 3 week course of treatment, with the preferred agent being doxycycline 100 mg BID. While effective in treating the systemic symptoms and proctocolitis associated with LGV, the lymphadenopathy may be slow to respond, and there may be little beneficial effect of treatment on the late complications described above. ■

References

1. San Francisco Monthly STD Report (Data for November 2004); report prepared December 22, 2004.
2. Gullion J, et al. HAN Advisory, Texas Department of State Health Services, December 23, 2004.
3. Stamm WE, et al. *Chlamydia trachomatis* (Trachoma, Perinatal Infections, *Lymphogranuloma Venereum*, and Other Genital Infections).
4. Mandell, et al. Principles and Practice of Infectious Diseases. Elsevier. 2005;2239-2255.

Hamster-Bite Fever?

ABSTRACT & COMMENTARY

Synopsis: *A child developed tularemia after being bitten by a pet hamster.*

Source: CDC. Brief Report: Tularemia Associated With a Hamster Bite—Colorado, 2004. *MMWR.* 2005;53:1202-1203.

A COLORADO FAMILY PURCHASED 6 HAMSTERS from a pet store, all of whom died within a week from a diarrheal illness. One, however, managed to bite a 3-year-old child on the index finger before dying. One week later, the child developed fever and painful left axillary lymphadenopathy, as well as sloughing of skin at the site of the bite. The child was given amoxicillin/clavulanic acid without success, and 7 weeks after the onset of illness, the left axillary lymph node was excised. *Francisella tularensis* was recovered from the tissue, and the patient was found to have a convalescent titer to this organism of 1:4096. He was successfully treated with ciprofloxacin.

COMMENT BY STAN DERESINSKI, MD, FACP

Francisella tularensis is a small, aerobic, catalase-positive, pleomorphic, Gram-negative coccobacillus. It is infrequently detected in Gram stains of clinical material. In addition, its growth in culture requires the presence of a sulfhydryl source and, as a consequence, it will not be recovered on most routinely used solid media in the absence of supplementation. As a consequence, its isolation requires a high index of clinical suspicion, which is important to communicate to the clinical microbiology laboratory. This communication is also of importance because the organism presents a significant biohazard in the laboratory. Infection may be confirmed with serological studies.

While *F. tularensis* infects a large spectrum of both vertebrates and invertebrates, rabbits and rodents are most important. Transmission to humans occurs most frequently as the result of contact with contaminated animal products or insect bite, although it may also occur via aerosol, contact with contaminated environment or, as in the case summarized here, via animal bites. In experimental systems, as few as 10 organisms are capable of causing disease.

Although overlap of the syndromes is not uncommon, 6 clinical forms of tularemia are typically described: ulceroglandular, glandular, oculoglandular, pharyngeal, typhoidal, and pneumonic. The child whose illness is summarized here would be classified as having the glandular form. The axilla is the most frequent site of adenopathy in rabbit-associated human tularemia, while the inguinal lymph nodes are most frequently involved in tick-associated disease—presumably reflecting the lymphatic drainage of the sites of inoculation.

Texts still recommend streptomycin as the treatment of choice for patients with tularemia, with gentamicin as an alternative. Doxycycline therapy has apparently been associated with failures. The organism is susceptible in vitro to fluoroquinolones, and ciprofloxacin therapy was successful in the case reviewed here. ■

Rat-Bite Fever

ABSTRACT & COMMENTARY

Synopsis: *Two rapidly fatal cases of rat bite fever due to Streptobacillus moniliformis are described.*

Source: CDC. Fatal Rat-Bite Fever—Florida and Washington, 2003. *MMWR.* 2005;53:1198-1202.

A 52-YEAR-OLD FEMALE PET STORE EMPLOYEE presented to a Florida Emergency room with a 2-day history of a febrile illness. She was hypotensive and, despite receiving antibiotic therapy in an ICU setting, died within 12 hours of admission. Two months later, a previously healthy 19-year-old woman was dead on arrival at a Washington state hospital. Friends reported that she had had a febrile illness for the previous 3 days. The first patient had been bitten by a rat in her pet store 4 days prior to admission and the second lived in an apartment with 9 pet rats.

Peripheral blood smears of the 52-year-old woman revealed filamentous bacteria within neutrophils. Specially performed blood cultures yielded a bacterium that was biochemically identified as *Streptobacillus moniliformis*, with confirmation by 16S rRNA analysis. While postmortem blood and tissue from the 19-year-old were culture negative, clusters of filamentous bacteria were identified in sections of liver and kidney by use of a silver stain, and 16S RNA sequence amplification identified these organisms as *S. moniliformis*.

COMMENT BY STAN DERESINSKI, MD, FACP

Rat bite fever caused by *S. moniliformis* typically begins with the abrupt onset of fever and chills, together with myalgias, arthralgias, and headache. An erythematous macular rash, most prominent on the extremities and involving the soles and palms, develops in most patients. Frank arthritis, most commonly affecting the knees, wrists, and elbows, may occur. Septic complications may occur at other sites. These include endocarditis, myocarditis, meningitis, and pneumonia. As in the 2 cases summarized here, the rapid onset of sepsis, culminating in death, may uncommonly occur. It is estimated that the case fatality in untreated patients is 10%. A similar illness, also called rat bite fever, is caused by a spirochet, *Spirillum minus*. This disease, almost exclusively identified in Asia, is also called sedoku.

S. moniliformis is a pleomorphic facultatively anaerobic Gram negative bacillus. Its morphologic variability in culture ranges from single cells to filamentous forms, which may resemble a string of beads as the result of central swelling of individual cells. In vitro cultivation requires supplementation with, eg, blood or serum. The CDC recommendations for diagnosis are contained in Table 1.

S. moniliformis is part of the normal upper respiratory flora of rodents. One-third of patients do not have a history of a rat bite, and infection may occur as the result of non-bite contact with infected rats or their excreta. A form of illness called Haverhill fever (erythema arthriticum epidemicum) results from ingestion of the organisms, most frequently in contaminated raw milk.

Penicillin G remains the treatment of choice (*see Table 1*). The CDC lists tetracycline and streptomycin as alternatives.

These cases were identified by the CDC Unexplained Deaths and Critical Illnesses (UNEX) Project. UNEX coordinates surveillance for unexpected deaths possibly attributed to infection throughout the United States State and local health departments may contact UNEX for assistance with evaluation of unexplained deaths in their jurisdictions. Infectious disease clinicians should encourage them to do so. ■

Table 1

CDC Recommendations For Diagnosis and Treatment of Rat Bite Fever Due to *Streptobacillus moniliformis*.

Diagnosis

Blood or synovial fluid culture, collected in tubes without sodium polyanethol sulfonate (SPS). Inoculate solution of sterile normal rabbit serum and incubate in humid environment with 5%-10% CO2 at 98.6°F (37°C). Hold cultures >5 days.

Pleomorphic bacilli in Gram-,Wright-,or silver-stained blood smears or tissues supports diagnosis.

For assistance, contact a state public health laboratory or CDC Meningitis and Special Pathogens Branch, telephone 404-639-3158.

Treatment

Intravenous penicillin, 1.2 million units/day for 5-7 days, followed by oral penicillin or ampicillin 500 mg four times a day for 7 days if improvement is observed.

Oral tetracycline 500 mg four times a day or intramuscular streptomycin 7.5 mg/kg twice daily are alternatives.

Probiotics For Preventing Infectious Diarrhea in Infants

ABSTRACT & COMMENTARY

Synopsis: *A double-blind, placebo-controlled, randomized trial of infants fed a formula supplemented with probiotics showed a mild reduction in the days and episodes of fever, and the days and episodes of diarrhea, with no effect on respiratory tract illnesses.*

Source: Weizman Z, et al. Effect of Probiotic Infant Formula on Infections in Child Care Centers: Comparison of 2 Probiotic Agents. *Pediatr*. 2005;115:5-9.

A DOUBLE-BLIND, PLACEBO-CONTROLLED, RANDOMIZED trial of 201 healthy, formula-fed infants 4-10 months of age in 14 child care centers was conducted in the Beer-Sheva area of Israel. Infants were randomly assigned to receive formula supplemented with *Bifidobacterium lactis*, *Lactobacillus reuteri*, or no probiotic for 12 weeks. The concentration of microorganisms in supplemented formula, which was humanized cow's milk formula, was 1×10^7 colony forming units per gram of formula powder, with a mean daily ingested dose of 1.2×10^9 colony forming units per day.

There were no significant differences among groups at randomization for age, birth weight, gestational age, gender, breastfeeding before the study, mean number of siblings, parental smoking, crowding (> 3 persons in a room), or presence of a household pet. There were no differences among groups during the study in the mean daily formula volume, daily number of meals, regurgitation or vomiting episodes, or adherence. There was no effect on respiratory tract illnesses. No adverse events were noted. There were no outbreaks of diarrhea during the study, and no cases of antibiotic-associated diarrhea.

Control infants had significantly more febrile episodes compared to infants fed formula supplemented with *B. lactis* or *L. reuteri* (0.41 vs 0.27 vs 0.11), more episodes of diarrhea (0.31 vs 0.13 vs 0.02), and more days of diarrhea (0.59 vs 0.37 vs 0.15). The *L. reuteri* group, compared to the control and *B. lactis* groups, had significantly fewer days with fever (0.17 vs 0.83 vs 0.86), less visits to the clinic (0.23 vs 0.55 vs 0.51), less absences from child care (0.14 vs 0.43 vs 0.41), and fewer prescriptions of antibiotics (0.06 vs 0.19 vs 0.21).

COMMENT BY HAL B. JENSON, MD, FAAP

Probiotics, which are viable nonpathogenic bacteria, are used to colonize the intestinal tract to modify intestinal microflora and provide beneficial effects for the host. Breastfed infants normally acquire *Bifidobacterium* and *Lactobacillus* species in the first week of life. These probiotic species are regarded as safe to use clinically because they occur naturally in the intestine. Formula-fed infants have more *Escherichia coli* and other Gram-negative bacilli, and fewer *Bifidobacterium*. In this study, there was greater benefit from *L. reuteri* than from *B. lactis*. *Lactobacilli* are an important part of the healthy infant flora, and are probably responsible for much of colonization resistance. *Lactobacilli* are purported to modulate immune response, although much knowledge about the specific effects on the immune system is lacking.

There are very few randomized controlled trials of probiotics for the prevention of infections in healthy children. These results show that children who are not breastfed and who attend child care, both of which increase the risk of gastrointestinal and respiratory tract infections, may benefit from probiotic supplementation. As expected, there was no effect on respiratory tract illnesses. However, some of the statistically significant differences in this study on gastrointestinal tract infections were very minor, such as < 1 day for differences induration of fever and diarrhea, and < 1 episode of diarrhea over a 12-week period. Longer studies should accentuate the benefits. These data add to the body of evidence that probiotic therapies should not be summarily dismissed. Further studies may confirm that they provide a safe and effective means of prophylaxis for diarrhea, but questions about long-term dosing and safety, practicalities of administration, and secondary consequences would have to be addressed by longitudinal studies. ■

Ribavirin For Hantavirus Cardiopulmonary Syndrome. . . It's Back to the Drawing Board

ABSTRACT & COMMENTARY

Synopsis: *Although a definitive answer could not be reached because of small sample size, no evidence of benefit from the treatment of hantavirus cardiopulmonary syndrome with ribavirin was detected.*

Source: Mertz GJ, et al. Placebo-Controlled, Double-Blind Trial of Intravenous Ribavirin For the Treatment of Hanatavirus Cardiopulmonary Syndrome in North America. *Clin Infect Dis.* 2004;39:1307-1313.

After only 36 patients were enrolled in more than 5 years in a multicenter, randomized trial comparing ribavirin therapy to placebo in patients with hantavirus infection in the United States the study was terminated and the results analyzed. Immunocompromise and shock were among the exclusion criteria.

Only 23 of the 36 proved to have serological evidence of hantavirus infection; 10 received ribavirin and 13 received placebo. Although attempts were made to include patients with hantavirus prodromal syndrome, all 23 with proven infection had hantavirus cardiopulmonary syndrome. The introduction of extracorporeal membrane oxygenation (ECMO) during the trial and its use in 7 patients further compromised (or, at least, complicated) the data analysis. The proportion who survived to 28 days and did not require ECMO was 70% in those assigned ribavirin and 62% in placebo recipients. Two patients in each group died, including 3 of 7 patients treated with ECMO. A futility analysis

based on the trends observed indicated that more than 1000 patients would have to be enrolled to have a chance of demonstrating a significant difference between treatment groups.

COMMENT BY STAN DERESINSKI, MD, FACP

Hantaviruses, including Sin Nombre, the virus prevalent in the southwestern United States (most of the patients in this study were enrolled in New Mexico), are susceptible to ribavirin in vitro. A placebo controlled randomized trial in China, published 14 years ago demonstrated significantly improved survival with ribavirin treatment in patients with hemorrhagic fever with renal syndrome, which is caused by Hantaan virus.[1]

In contrast to the disease in Eurasia in which the kidneys are a prime target, the North American hantaviruses commonly cause pulmonary involvement. While such involvement has led to the commonly used sobriquet of hantavirus pulmonary syndrome, the authors of the study reviewed here prefer the term hantavirus cardiopulmonary syndrome because they indicate that almost all the fatalities are caused by cardiogenic shock.

The infection generally starts abruptly, with influenza-like symptoms followed, after several days, with the appearance of a non-productive cough and breathlessness, heralding the onset of pulmonary edema. Hypotension, with associated hemoconcentration, may occur. Hemodynamic measurements reveal, consistent with cardiac failure, a low cardiac index and an elevated systemic vascular resistance—findings directly opposite to those seen in septic shock. The fatality rate is approximately 36%.

The earliest laboratory finding that distinguishes this infection is thrombocytopenia. Leukocytosis with the appearance of early forms is characteristic, as is the appearance of reactive lymphocytes in the peripheral blood contemporaneously with the development of pulmonary edema. It is reported that the combination of thrombocytopenia together with the appearance of myelocytes and immunoblasts in the peripheral blood is strong evidence of hantavirus infection in the proper setting.

This trial represented a valiant attempt to perform a randomized clinical trial in the treatment of an infection that occurs at low frequency and for which there was no effective rapid diagnostic test during the prodromal phase. The patients with proven hantavirus infection enrolled in this trial had advanced severe disease. This is documented by the fact that the median time from first administration of drug or placebo to either death or initiation of ECMO was 4 hours for the former and 24 hours for the latter. Thus, while the investigators conclude that ribavirin was not of benefit in these critically ill patients, the possibility of benefit during the prodromal phase cannot be excluded. Early sensitive and specific diagnosis, however, remains elusive. ■

Reference

1. Huggins JW, et al. Prospective, Double-Blind, Concurrent, Placebo-Controlled Clinical Trial of Intravenous Ribavirin Therapy of Hemorrhagic Fever With Renal Syndrome. J Infect Dis. 1991;164:1119-1127.

Announcement

Infectious Disease Alert Welcomes 2 New Editors.

Dr. Jessica Song received her PharmD at the University of California School of Pharmacy after receiving a masters degree in physical chemistry Johns Hopkins University. She performed her residency and fellowship at Hartford Hospital and the University of Connecticut. She is an assistant professor of pharmacy practice at the University of the Pacific and is pharmacy clerkship coordinator at the Santa Clara Valley Medical Center in San Jose, California.

Dr. Dean Winslow received his MD at the Jefferson Medical College and trained in internal medicine at the Medical Center of Delaware before completing a research fellowship in infectious diseases at Ochsner Clinic and Ochsner Foundation Hospital in New Orleans. After a period in private practice, he worked in the pharmaceutical industry before becoming a clinical professor of medicine in the Division of Infectious Disease and Geographic Medicine at Stanford University, where he is co-Director of the Infectious Diseases Fellowship Training Program. He is currently chief of the division of AIDS medicine at the Santa Clara Valley Medical Center in San Jose, CA. ■

CME Questions

4. What is the rate of congenital HHV6 infection?

a. Rare
b. 1%
c. 3%
d. 5%
e. 7%

5. Appropriate treatment regimens for lymphogranuloma infection include (more than one may be correct):

a. doxycycline 100 mg BID for 7 days.
b. azithromycin one gram single dose.
c. doxycycline 100 mg BID for 21 days.
d. erythromycin base 500 mg QID for 21 days.

6. Which of the following is correct?
a. Doxycycline is the treatment of choice for tularemia.
b. *Francisella tularensis* requires a sufhydryl source for in vitro cultivation.
c. *F. tularensis* is readily detected in Gram stains of clinical material.
d. Tularemia is infrequently encountered because of the high inoculum (>106 organisms) required for infection.

7. Which of the following is correct?
a. The chief cause of rat bite fever in the United States is *Spirilum minus*.
b. Haverhill fever is caused by *Spirilum minus*.
c. Sedoku is caused by *Spirilum minus*.
d. *Spirilum minus* is predominantly found in Asia.

8. Probiotic supplementation of infant formula reduces the burden of which illness?
a. Impetigo
b. Common colds
c. Otitis media
d. Diarrhea
e. None of the above

9. Which of the following is a typical triad of findings in the peripheral blood of patients with hantavirus pulmonary syndrome?
a. Thrombocytopenia, leukocytosis with myelocytes and reactive lymphocytes (immunoblasts).
b. Thrombocytopenia, leucopenia, lymphocytosis.
c. Thrombocytosis, leukocytosis, lymphopenia.
d. Thrombocytosis, leukocytosis without a left shift to early forms, lymphocytosis.

Answers: 4. (b); 5. (c&d); 6. (b); 7. (d); 8. (d); 9. (a)

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In Future Issues:

11th International Symposium of Staphylococci & Staphylococcal Infection

UPDATES

By Carol A. Kemper, MD, FACP

Rev. Deresienski Stops Communion!

New York Times, November 28, 2004;18.

TWO YEARS AGO, WITH THE ADVENT of SARS in the world, Catholic priests in Toronto held mass without communion, fearing the chalice may be a source for transmission for the virus. Now, because of this year's flu vaccine shortage, the Roman Catholic Diocese in Burlington, VT. has taken the unprecedented step of withholding communion from parishioners, and has asked parishioners not to hug, kiss, or shake hands when they make the sign of peace. In addition to the parish of Rev. Stanley Deresienski (!) in Brattleboro, VT., about 130 churches and 148,000 parishioners are affected. The edict, which was issued by Bishop Angell (!!) began October 31, 2004, and is expected to end on Easter Sunday, March 27, 2005 (although whether the influenza season will be done by then is an open question).

Many people have embraced the change, according to the New York Times, not wanting to share a cup or shake hands "with a visibly sick person." One parishioner, who supported the ban, was quoted as saying, "There's science and the germ theory, and there's also our faith. God doesn't discount the germ theory."

Whether common communion presents a public health hazard to participants has been a long-standing, but poorly substantiated concern. While it would not be surprising if there was low-level risk of transmission of certain respiratory illnesses during communion, such as the common cold virus, herpes simplex, or even strep throat, various studies have examined this question and found no significant risk of contagion, and no significant outbreaks of illness have been linked to sharing the chalice. One Texas women died of meningococcemia in 2002 after drinking from a common communion cup at Catholic mass, but the connection was never confirmed. Unfortunately, the alcohol content of communion wine is probably insufficient to function as a disinfectant, although there may be some theoretical benefit (a teleologic benefit?) to using real wine and not grape juice. Common sense dictates that people with active herpes, the flu, or other contagious respiratory illnesses refrain from taking common communion. Whatever happened to faith and washing hands? ■

Environmental Mimics of Chemical Warfare

Claborn DM. *Military Medicine* 2004; 169:958-961.

SYMPTOMS OF CHEMICAL WARFARE are varied, but can include skin rashes and blistering, burns, increased salivation, muscle tremors and weakness, and paralysis. However, a number of other exposures and infectious diseases can produce similar signs and symptoms, including various animal and insect bites, plant exposures, ingestion of certain marine toxins, cleaning agents, and pesticides. A recent example of the confusion that can occur in the battlefield was an outbreak of conjunctivitis and skin blisters that occurred in a group of marines during a military exercise. Military medical personnel could not, at first, identify the cause of the outbreak. Despite the fact that this occurred in Arizona, where there was no credible threat of chemical exposure, and the marines were quite stable, several marines, including at least 1 field level officer, were not assuaged, and threatened to seek civilian care. They were convinced they had been victim to some kind of chemical attack, similar to that seen during their training sessions on chemical warfare. Ironically, the marines had suffered a variation of a chemical attack: they had been hit by a band of rove beetles, flushed from their burrows by heavy rains. The rove beetle secretes a noxious toxin when it rubs up against you, resulting in large skin blisters and blebs and conjunctivitis.

Other interesting examples of things that can mimic nerve agents (such as organophophates) include the bites of certain snakes (such as cobras, kraits, and elapids), which can cause heavy salivation, tremors, paralysis and death; tick paralysis, which causes progressive numbness and paralysis; botulism, tetanus, and rabies. In addition, military personnel should keep in mind that agricultural products in other parts of the world may be over-treated with insecticides, pesticides, and fungicides, and could result in true organophosphate poisoning or other toxin ingestion. It is all just a matter of the level of exposure.

Skin conditions resembling vesicating warfare agents (like mustard and Levisite) include contact dermatitis, impetigo, herpes simplex or zoster, poison ivy, photosensitivity

and allergic reactions, and thermal or chemical burns. Both rove and meloid beetles (known as blister beetles) can cause impressive skin blistering and conjunctivitis—these can be found in Africa, Southeast Asia, Australia, and South America. Caterpillars, millipedes, and spiders can cause severe urticaria (mimicking phosgene agents), blisters, eschars and necrotizing skin lesions. Although one would suspect these would result in isolated cases, and not affect a whole platoon, reports document the occurrence of caterpillar-induced urticaria occurring simultaneously in thousands of soldiers in the Middle East, when the desert wind kicked up a hive of caterpillars and scattered their spines in the wind.

As Claborn acknowledged, "the threat of chemical warfare, whether real or perceived, has a lasting and adverse impact on health." Military personnel should be trained to understand the potential environmental causes of various signs and symptoms, and be able to differentiate between the effects of chemical warfare agents and other illness. This includes understanding the epidemiology and geographic distribution of various diseases, being able to do a proper epidemiologic investigation, and not immediately assuming the worst. ■

Malaria in Airline Crew Members

Byrne NJ, et al. *J Travel Medicine.* 2004;11:359-363.

Byrne et al examined the risk of falciparum malaria in airline crew members who lay-over in malaria-endemic areas. Apparently, a number of British airlines are opening new routes to Africa that involve layovers, although longer layovers are increasingly uncommon because of the need for greater business efficiency. Presumably, most British crew members are non-immune to falciparum malaria.

Various destinations, hotels, potential risk behaviors, and the number of nights of layover were examined. From 1994 to 2003, a total of 5 cases of falciparum malaria occurred in airline personnel; none resulted in death. Each of the individuals had engaged in some kind of risk behavior that increased their level of exposure, including 4 who dined al fresco and 1 who took advantage of an overnight safari. Two pilots were affected—both Boeing 767 pilots coming out of Entebbe and Dar es Salaam. Three crew members were affected on flights coming out of Accra, Lusaka, and Abidjan. Based on these cases, the annual risk to flight personnel for layovers in sub-saharan Africa was estimated at 1.6 per 100,000 nights (not bad, considering you wouldn't want your pilot to come down with falciparum during flight).

By and large, crew members were good about using personnel protective equipment, such as proper clothing and DEET, although previous studies have documented less than 10% compliance with chemoprophylaxis. Airports were generally air-conditioned, and air conditioned transport to and from hotels was provided for all crew. All hotels were air-conditioned and centrally located in large urban areas, thereby reducing the risk. The risk was reduced even further in certain cities like Lagos, where personnel were not allowed to venture outside because of security risks (not a fun layover). Pilots who do their own walk-abouts and inspect the plane prior to take-off may be at slightly increased risk, although this was felt to be negligible.

Based on these data, Byrne and colleagues recommend that airline crews be more strongly educated about the use of insect repellent and protective clothing, and the avoidance of certain activities (sports and dining outdoors) between dusk and dawn. Prophylaxis with atovaquone-proguanil should only be recommended for those airline crew with non-standard layovers or stays in areas remote from large urban centers. ■

Paradoxical Effect of High-Dose Caspofungin

Stevens DA, et al. *Antimicrob Agents Chemother.* 2004;48:3407-3411.

Caspofungin, which is a non-competitive inhibitor of fungal cell wall glucan synthesis, is fungicidal in vitro against *Candida* species. Documented in vitro resistance has been rare, even after prolonged treatment, although clinical failure occurs. However, Stevens et al identified some clinical Candida albicans isolates that exhibited paradoxical turbid growth in broth at very high concentrations of caspofungin, far above their MICs. The frequency of this phenomena in clinical isolates submitted for susceptibility testing was 16%. In addition, among a select group of isolates, tested at concentrations up to 50 mcg/mL, 53% showed a mini-paradoxical effect; in other words, no turbid growth occurred but the isolates demonstrated incomplete cidal activity. Progeny of these isolates, grown in the absence of drug, did not demonstrate total resistance, but the paradoxical affect, similar to the parent, could be demonstrated 15 of 15 times. Interestingly, the addition of fluconazole, which acts synergistically with Caspofungin, eliminated the effect. Stevens and colleagues postulate that exposure to high drug concentrations could derepress or activate unknown resistance mechanisms, which could have clinical consequences. ■

PHARMACOLOGY WATCH

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.*

Statins and the Incidence of Rhabdomyolysis

The most commonly prescribed statins have a low incidence of rhabdomyolysis, according to the results a new study of more than 250,000 patients. Atorvastatin, pravastatin, and simvastatin were found have very low and virtually indistinguishable rates of rhabdomyolysis of 0.44 per 10,000 person-years (95% CI, 0.20-0.84). The data were obtained from 11 managed care health plans across United States from January 1, 1998, through June 30, 2001. Cerivastatin (Baycol-Bayer), which was withdrawn from the market in 2001, was found have a much of a higher rate of rhabdomyolysis, 5.34 cases per 10,000 person-years (95% CI, 1.46-13.68). The concomitant use of a fibrate with atorvastatin, pravastatin, or simvastatin was found to have increased the rate to 5.98 (95% CI, 0.72-216.0), while use of a fibrate with cerivastatin dramatically increased the rate to 1035 cases per 10,000 person-years of treatment (95% CI, 389-2117), or nearly 1 in 10. Older patients, especially those with diabetes, were found to have higher rates of rhabdomyolysis. The authors conclude that the most commonly prescribed statins have a low incidence of rhabdomyolysis, which is increased with the addition of a fibrate (*JAMA.* 2004;292:2585-2590).

The study confirms the safety of the most commonly used statins, but raises issues regarding the post marketing surveillance of cerivastatin. These concerns were addressed in a review in the same issue of *JAMA* regarding the potential conflict of interest once initial reports of rhabdomyolysis were reported to the company, and the delay in the availability of this information to consumers. The critique is accompanied by Bayer's rebuttal (*JAMA.* 2004;292:2622-2631, 2643-2646, 2655-2657, 2658-2659), which makes fascinating reading given the recent criticisms of the FDA and post marketing surveillance regarding coxibs.

A Crackdown on Importation of Drugs

Officials in both the United States and Canada are taking steps to crack down on the importation of prescription medications across the border. A New York District Court issued an injunction in December against Canada Care Drugs Inc., which gave the FDA authority to inspect the company to assure that they no longer import drugs to American consumers. The FDA had petitioned the court to take this action based on a sting operation run by the agency. FDA investigators purchased Neurontin and Sporanox through Canada

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Care. Instead of Neurontin, investigators received APO-gabapentin and NOVO-gabapentin, formulations of the drug that are not subject to FDA scrutiny in this country. The Sporanox shipment included 84 tablets of the correct drug, but investigators felt that the amount was excessive, determining that patients should not take Sporanox continuously without checking with their physician. The court is scheduling a trial date for Canada Care, an action that is sure to put other Canadian importation companies on alert. Meanwhile, the Canadian government is also cracking down on Internet pharmacies that export drugs to the United States without evaluation by Canadian doctors. The government is considering making it illegal for Canadian doctors to countersign prescriptions from other countries. This move in Canada is prompted by concern over shortages of drugs for Canadian citizens, especially given threats by American drug companies to withhold additional shipments of drugs to Cananda, where they have strict price controls, knowing that many of these drugs may come back to the US market were there are no price controls. These moves are strongly supported by PhRMA, the powerful pharmaceutical advocacy group.

FDA Actions

The FDA has approved a new non-benzodiazepine hypnotic for the treatment of insomnia. Sepracor, a company that specializes in marketing active isomers of currently approved drugs, has received approval to market eszopiclone, the active (S)-isomer of zoplicone, which is available outside the United States. The drug is similar to zopidem (Ambien) and zaleplon (Sonata) in that it has a lower incidence of tolerance, dependence, and withdrawal symptoms than benzodiazepines. Based on a 6-month, double-blind, placebo-controlled safety and efficacy trial, the FDA decided not to limit eszoplicone's indication to short-term use. Eszoplicone will be available in 1mg, 2mg, and 3mg tablets, and will be marketed in United States under the trade name Lunesta. Sepracor is also studying the drug for treatment of insomnia in patients with depression or pain, and in peri-menopausal women.

Novartis has received approval to market darifenacin extended release tablets for the treatment of overactive bladder with symptoms of urging incontinence, urgency, and frequency. The drug is an M3 (muscarinic) receptor blocker that increases urinary capacity and decreases urinary episodes and frequency of incontinence, along with feelings of urgency. Darifenacin, which is already available in Europe, will be marketed in the United States as Enablex.

Drugs approved under the FDAs accelerated approval program are often approved on the basis of surrogate end points, such as tumor markers that would indicate the likelihood of clinical benefit. The FDA, however, requires that cancer drugs in particular, must document clinical benefit in subsequent studies to remain marketable. A recent case-in-point is AstraZeneca's gefitnib (Iressa), which was approved for treatment of non small cell lung cancer in patients who failed other courses of cancer therapy. A recent study of gefitnib involving nearly 1700 patients failed to show a survival benefit better than placebo. The drug, which was initially approved in 2003, now faces a FDA review to determine whether the drug will be removed from the market. In a letter to physicians, AstraZeneca "urges you to consider other treatment options in recurrent non small cell lung cancer patient population." In the meantime, Genentech and Roche's erlotinib (Tarceva), which has shown survival benefit for the same patient population, remains a viable option.

The FDA has issued a Public Health Advisory regarding the use of anti-inflammatories including COX-2 inhibitors because of recent indications that the drugs may increase the risk of cardiovascular disease and stroke. The agency is requiring evaluation of all prevention studies that involve the COX-2 inhibitors celecoxib (Celebrex) and valdecoxib (Bextra) to ensure that adequate precautions are in place. Several prevention studies regarding potential benefit of these drugs on colon polyps and Alzheimer's disease are either in progress or planned in the near future. Meanwhile, the agency is recommending that physicians should prescribed Celebrex or Bextra with caution, particularly in patients at risk for cardiovascular disease, and should weigh the risk vs benefits.

The FDA is also recommending that consumers should use over-the-counter anti-inflammatories in strict accordance with the label directions, taking them for no longer than 10 days without consulting a physician. ■