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Corticosteroids and Adult Meningitis

ABSTRACT & COMMENTARY

Synopsis: Adjunctive therapy with dexamethosone, initiated immediately before or with the first dose of antibiotic, significantly improved outcomes in adults with pneumococcal meningitis.

Source: de Gans J, et al. Dexamethasone in adults with bacterial meningitis. *N Engl J Med*. 2002;347:1549-1556.

DE GANS AND COLLEAGUES IN THE NETHERLANDS randomized adults with suspected bacterial meningitis to receive, in addition to amoxicillin, dexamethasone (10 mg IV q.6h. for 4 d, initiated 15-20 min) before first antibiotic administration. After an interim analysis was conducted on approximately one half of the total enrollment, the protocol was amended to allow administration of the dexamethasone simultaneously with the antibiotic and to allow investigators to follow local guidelines for choice of empirical antibiotic therapy; both changes were made to accelerate enrollment.

Of the 301 patients enrolled, 159 were assigned dexamethasone and 144 assigned placebo were included in the final analysis of outcome at 8 weeks. The groups were comparable at the time of enrollment. Approximately one fifth of the patients had a negative-CSF culture but were included in the analysis because of other findings consistent with a bacterial etiology of their meningitis. *Streptococcus pneumoniae* and *Neisseria meningitidis* each accounted for approximately one-third of the positive cultures. CSF from 6 patients yielded *Listeria monocytogenes*, 4 *Haemophilus influenzae*, 3 *Staphylococcus aureus*, and 1 each of *Escherichia coli*, *Klebsiella pneumoniae*, *Capnocytophaga canimorsus*, and a *Corynebacterium* species.

A favorable outcome was defined as the presence of mild or no disability, with the patient able to return to work or school. Dexamethasone therapy was associated with a significant reduction in the risk of an unfavorable outcome (RR, 0.59; 95% CI, 0.37-0.93; $P = 0.03$), as well as a reduction in mortality (RR, 0.48; 95% CI, 0.24-0.96; $P = 0.04$). The effects were most strik-

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ing in the patients with pneumococcal meningitis among whom assignment to dexamethasone therapy was associated with unfavorable outcome in 26% vs 52% in the placebo group (RR, 0.50; 95% CI, 0.30-0.83; P = 0.006). The mortality rate was reduced from 34% to 14%. In contrast, patients with meningococcal meningitis, with unfavorable outcomes in only 8% and 11%, derived no apparent benefit from dexathasone therapy; this was also true of those with other organisms on culture (although the number of these was quite small) and those with negative cultures.

Dexamethasone therapy was well tolerated, although 2 recipients of this drug were withdrawn from the study because of severe hyperglycemia, as were one each for suspected stomach perforation (that, in fact, was not present) and agitation and flushing. In addition, 1 dexamethasone recipient developed gastrointestinal bleeding and perforation of the stomach.

Susceptibility testing was performed on 77 of the 108 *S pneumoniae* isolates; all had a penicillin MIC < 0.1 µg/mL. One of 80 meningococcal isolates tested had intermediate resistance to penicillin. The initial empiric antibiotic therapy provided adequate coverage in 97% of the dexamethasone and 98% of the placebo group with positive cultures.

COMMENT BY STAN DERESINSKI, MD, FACP

While some level of controversy has persisted regarding the benefit of adjunctive corticosteroid therapy in pediatric meningitis, there is reasonable evidence that dexamethasone administration is associated with a reduction in neurological sequelae in children, most particularly sensorineural hearing loss in *H influenzae* meningitis. The evidence of benefit in pneumococcal meningitis, now the most common form of this infection in the United States, and the evidence of benefit in adults has been much weaker. This study clearly demonstrates a benefit to dexamethasone therapy in adults with pneumococcal meningitis. In contrast, no benefit could be demonstrated in patients with meningococcal meningitis, an infection with a much better prognosis.

The choice of amoxicillin by de Gans et al at the initiation of the trial was based on the susceptibility data prevalent in The Netherlands at the time. The current recommendation in the United States for empiric treatment of bacterial meningitis, dictated by the increasing antibiotic resistance in *S pneumoniae*, is the use of ceftriaxone plus vancomycin. Some also recommend the addition of rifampin, particularly in patients given corticosteroids because of concerns about their potential negative effect on vancomycin accumulation in the CSF, a concern which, based on human data, may be unwarranted.

de Gans et al, as well as Tunkel and Scheld in an accompanying editorial, recommend the routine use of dexamethasone, given immediately before or with the first dose of antibiotic, as adjunctive therapy in adults with suspected pneumococcal meningitis.[1] Tunkel and Scheld recommend against their use in patients who have already received antibiotics or those in septic shock. They further recommend that, if the meningitis is found to not be caused by *S pneumoniae*, administration of dexamethasone be discontinued. Tunkel and Scheld also raise concern regarding the applicability of these findings to treatment of infections caused by pneumococci that are ceftriaxone resistant. These seem reasonable recommendations and concerns, although the caveat against corticosteroid use in

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patients with septic shock, which is based on a study demonstrating a trend, not statistically significant, toward poorer outcomes in septic shock patients in the absence of reduced adrenalcortical reserve, may be questionable.[2,3] ■

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Group A Streptococcal Infection: An Occupational Hazard for Health Care Workers

ABSTRACT & COMMENTARY

Synopsis: *A patient with group A streptococcal respiratory and soft tissue infection was the source of an outbreak involving 24 health care workers.*

Source: Kakis A, et al. An outbreak of group A streptococcal infection among healthcare workers. *Clin Infect Dis*. 2002; 35:1353-1359.

A previously healthy 43-year-old woman presented to the emergency department with bullae involving her left breast. She had had the onset of fever and upper respiratory symptoms 3 days earlier. Over several hours the lesions of the breast began to coalesce and spread, followed by sloughing. She developed vomiting, diarrhea, renal failure, and respiratory distress. Chest X-ray showed pulmonary infiltrates. She was admitted to the critical care unit and underwent nasotracheal intubation. Group A streptococci (GAS) were isolated from blood, respiratory secretions, and soft tissue. She was treated with vancomycin, piperacillin-tazobactam, clindamycin, intravenous immuglobulin, and hemodialysis. On the sixth hospital day she underwent mastectomy; there was extensive tissue necrosis along with multiple abscesses. The patient ultimately died on hospital day 17.

On hospital day 4, 3 ICU nurses complained of sore throat and fever. Initial surveillance identified 20 symptomatic staff who had had direct patient contact. Of these, a total of 10 had positive pharyngeal cultures for GAS. Expanded culture surveillance of asymptomatic staff who had had patient contact identified a total of 24 culture-positive individuals, and 1 symptomatic physician who treated himself with penicillin before undergoing culture (he was included as a case). Isolates from the culture-positive staff were compared with the source patient's isolates by DNA typing. Twenty-three had had a DNA pattern identical to that of the patient. The employee with a different pattern had 2 children at home with GAS pharyngitis; her isolate was identical to that of her children. Thus, there were 24 nosocomial cases of GAS infection among hospital staff. All infected staff had had contact with the patient within the first 25 hours after presentation. All staff received treatment with penicillin or a macrolide. There were no secondary cases among patients or families.

■ COMMENT BY ROBERT MUDER, MD

This outbreak of GAS infection is unusual in that it involved a large number of hospital staff exposed over a relatively short period of time. One contributing factor may have been the streptococcal isolate. It was M type 1, and produced NADase. These factors have been associated with invasiveness and transmissibility.

The extensive nature of the patient's infection was no doubt a contributing factor, as well. In addition to extensive skin and soft tissue infection, she also had GAS pneumonia and underwent nasotracheal intubation shortly after admission. Thus, there would have been ample opportunity for both contact and respiratory droplet transmission. In a survey of compliance with infection control procedures done after the outbreak, staff caring for the patient nearly always wore gloves, but rarely wore gowns or masks. Although none of the staff involved in this outbreak had serious sequelae, a large number of employees required antibiotic therapy and a minimum of 24 hours of exclusion from work. Had there been secondary cases among patients, additional morbidity or even mortality might have occurred.

The most recent Centers for Disease Control (CDC) guidelines for isolation procedures in hospitals recommend droplet precautions (eg, private room and masks) for pediatric, but not adult, patients with GAS pharyngitis or pneumonia. Although one hesitates to draw sweeping conclusions, this report indicates that standard precautions may be inadequate for patients with pneumonia or very extensive soft tissue infection due to GAS. Given the potential seriousness of an outbreak of GAS in a hospital, I would recommend that such patients be managed with both contact and droplet precautions until at least 24 hours after institution of effective antibiotic therapy.

Editor's Note: A CDC workshop has published recommendations on prevention of invasive GABS disease among household contacts, as well as among postpartu-

ma and postsurgical patients (Clin Infect Dis. 2002; 35:950-959). The following is the kernel of their statement: "For household contacts of index patients, routine screening for and chemoprophylaxis against GAS are not recommended. Providers and public health officials may choose to offer chemoprophylaxis to household contacts who are at an increased risk of sporadic disease or mortality due to GAS. One nosocomial postpartum or postsurgical invasive GAS infection should prompt enhanced surveillance and isolate storage, whereas 2 cases caused by the same strain should prompt an epi- demiological investigation that includes the culture of specimens from epidemiologically linked health care workers." ■

MRSA & PVL: A Nasty Package

ABSTRACT & COMMENTARY

Synopsis: *A clonally related strain of S aureus that produces the Panton-Valentine leukocidin associated with severe cutaneous and pulmonary infections has been detected in a number of regions of France.*

Source: Dufour P, et al. Community-acquired methicillin-resistant *Staphylococcus aureus* infections in France: Emergence of a single clone that produces panton-valentine leukocidin. *Clin Infect Dis*. 2002;35:819-824.

DUFOUR AND COLLEAGUES IN LYON AND NANTES examined 593 isolates of *S aureus* that had been sent to their reference laboratory from throughout France for detection of toxin production. Eighty three (14%) of these were Panton-Valentin leukocidin (PVL)-positive and 14 of these were also methicillin-resistant. The median age of the patients was 13.5 years (range, 2.5 months to 69 years). Half the patients had cutaneous infections and 2 had bacteremic necrotizing pneumonia. Except for the presence of genes encoding LukF-LukD leukocidin, which were also present in all 14, genes for a wide range of additional toxins, including toxic shock and exfoliative toxins, were not detected. Genetic analysis indicated that the 14 isolates were related.

■ COMMENT BY STAN DERESINSKI, MD, FACP

PVL is a bicomponent toxin produced by some strains of *S aureus* that has been associated with community-acquired primary skin infections and severe necrotizing pneumonia. It is not, in contrast, associated with skin infections occurring secondary to cutaneous trauma, nosocomial pneumonia, or endocarditis.[1,2] The severity of illness associated with PVL-producing strains of *S aureus* can be assessed from a study of community-acquired pneumonia due to this organism. In that study, a comparison of 16 cases of PVL-positive *S aureus* pneumonia with 36 PVL-negative cases demonstrated an association of the former with prior influenza-like illness, younger median age (14.8 vs 70.1 years), greater severity, and higher mortality at 48 hours (63% vs 94%).[2]

Thus, it appears to be a virulence factor, allowing enhanced infectivity and the severity of *S aureus* infection in the absence of other promoters of invasion. In contrast, the LukF-LukD leukocidin, also detected in this study, is not highly associated with similar infections.

Exposure of leukocytes to PVL leads to formation of transmembrane octameric pores and release of a variety of inflammatory mediators, and intradermal injection of PVL in rabbits is associated with severe inflammatory lesions and skin necrosis.[3-5] Neutrophils are killed as the result of lysis by the toxin. Thus, these important effector cells, while contributing to the inflammatory response at the site of infection, are eliminated from participation in eradicating the infection.

Dufour et al report that their 14 related strains of PVL-producing MRSA were isolated from throughout France and were epidemiologically unrelated. This raises the fear that this "superadapted" strain containing an ominous confluence of an antibiotic resistance gene and a toxin gene may already be widespread there and, perhaps, elsewhere. ■

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Atopic Dermatitis: No Defensins Against *S aureus*

ABSTRACT & COMMENTARY

Synopsis: *Skin affected by atopic dermatitis fails to express antimicrobial peptides, possibly accounting for the almost universal presence of S aureus in these lesions.*

Source: Ong PY, et al. Endogenous antimicrobial peptides and skin infection in atopic dermatitis. *N Engl J Med*. 2002; 347:1151-1160.

ONG AND COLLEAGUES IN DENVER, SAN DIEGO, AND Los Angeles evaluated the role of endogenous antimicrobial peptides in protection against *Staphylococcus aureus* infection of the skin by examining the concentrations of cathecidins (LL-37) and human ß-defensin 2 (HBD-2) in skin biopsy samples from 8 patients with atopic dermatitis, 11 with psoriasis, and 6 healthy controls. Relative to patients with psoriasis, the concentration of both of these peptides was significantly reduced in both acute and chronic lesions of patients with atopic dermatitis, as was the expression of their relevant mRNAs. LL37 and HBD-2 were not detected in normal skin. In vitro studies demonstrated that LL-37 and HBD-2 synergistically killed *S aureus*.

COMMENT BY STAN DERESINSKI, MD, FACP

Up to 100% of patients with atopic dermatitis exhibit cutaneous colonization with *S aureus*.[1] While the pathophysiology of atopic dermatitis is poorly understood, production of a variety of staphylococcal toxins, especially those that act as superantigens have been suggested to play a role in contributing to the severity of the dermatitis.[2] In contrast, psoriasis is not associated with a significantly increased risk of staphylococcal infection.

The endogenous antimicrobial peptides are a part of the innate immune system and, among other things, act as a defense at our mucocutaneous interface with the outside world. Targeting the microbial cell membrane, they are variably active against some bacteria, fungi, and enveloped viruses. HBD-2, originally discovered in psoriatic lesional skin and expressed in ketinocytes associated with inflammatory cutaneous lesions, has potent activity against many Gram-negative bacteria and *Candida* spp., but does not have significant activity against *S aureus*.[3] This resistance appears to be related to the expression of a novel gene by this organism, *mpfR*, which is associated with a reduced negative membrane charge that presumably repulses the cationic antimicrobial peptides.[4] The study discussed here, however, demonstrates synergistic killing of *S aureus* at concentrations contained in psoriatic skin. Cathelicidins such as LL-37 appear to have characteristics similar to those of defensins and both types of protein also have chemotactic activity.

Thus, this study demonstrates that these cationic proteins are not expressed in normal skin, but are upregulated in psoriatic lesional skin. Atopic skin, despite the presence of inflammation and, almost invariably, *S aureus*, also fails to express these antimicrobial proteins, demonstrating an apparent failure of the innate immune system.

The role played by *S aureus* in atopic dermatitis remains unclear. As many as two thirds of associated strains produce superantigens, products that have been suggested, but not proven, to contribute to the pathophysiology of the disease. It would also be of interest to know the potental role of the Panton-Valentin leukocidin in this process. ■

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Helicobacter pylori Infection

ABSTRACT & COMMENTARY

Synopsis: *Helicobacter pylori is an exceedingly common inhabitant of the human stomach. The discovery of its role in the pathogenesis of peptic ulcer disease was revolutionary, but many questions remain about this organism and an appropriate medical approach to its presence.*

Source: Suerbaum S, Michetti P. *N Engl J Med*. 2002; 347: 1175-1186.

HELICOBACTER PYLORI WAS FIRST CULTURED 20 years ago, and it was soon recognized that peptic

ulcer disease might have an infectious pathogenesis. The presence of the organism is strongly correlated with socioeconomic conditions, ranging from 80% of middle-aged adults in developing countries to as little as 20% in industrialized countries. It seems likely that the decreased infection levels in the United States will eventually lead to the complete elimination of this infection from our society. *H pylori* in adults is usually chronic and resolves only with specific therapy, but children probably commonly spontaneously eliminate this infection. *H pylori* survives in the stomach using a number of protective mechanisms, including the production of urease-generated ammonia as a potent acid-neutralizing agent. Gastric inflammation is invariably produced by infestation with *H pylori*, and some infected patients have an autoantibody against the ATP-ase of parietal cells that may lead to gastric atrophy. Clinical outcome of infection is highly variable. Antral gastritis is associated with duodenal ulcers, and corpus gastritis seems related to gastric ulcers, gastric atrophy, intestinal metaplasia, and potentially gastric adenocarcinoma. MALT lymphoma is directly related to *H pylori* infection in genetically susceptible individuals. The incidence of cancer in Japan has been documented at 2.9% over 8 years. Nevertheless, it remains clear that most patients with *H pylori* infection never get ulcers, malt lymphoma, or gastric cancer. Controversy continues as to whether infection with *H pylori* protects against gastroesophageal reflux disease. Diagnostic tests for infection include the urea breath test, serological tests, and stool antigen testing. Serology cannot document either active infection or effective eradication. Trials have documented the substantial efficacy of triple therapy with PPI (b.i.d. except for rabeprazole that can be administered once daily) and 2 antibiotics (usually clarithromycin and amoxicillin) for *H pylori* eradication. Failure of eradication is common, often due to poor compliance with the initial regimen and may require quadruple therapy including a bismuth-based triple regimen plus a PPI or H2 receptor antagonist. Rifabutin plus amoxicillin and a PPI might be another option for second-line therapy. At the moment, the only completely accepted indications for *H pylori* eradication are ulcer disease and MALT lymphoma. Except in settings with a known high background prevalence of ulcer disease, empirical treatment of *H pylori* in dyspeptic patients is not recommended.

COMMENT BY MALCOLM ROBINSON MD, FACP, FACG

This area remains confusing, partly because many medical payers have urged empirical treatment of *H pylori* for economic reasons. The strong epidemiologic data for an inverse relationship between the presence of *H pylori* and gastroesophageal reflux disease would certainly suggest that physicians avoid seeking to diagnose *H pylori* in patients with primary GERD symptoms.

Strong international recommendations for aggressive eradication of *H pylori* to prevent cancer probably do not apply to North America. ■

Dr. Robinson is Medical Director, Oklahoma Foundation for Digestive Research; Clinical Professor of Medicine, University of Oklahoma College of Medicine, Oklahoma City, OK.

Pharmacology Update

Adefovir (Hepsera) for the Treatment of Chronic Hepatitis B Infection

By William T. Elliott, MD, FACP, and James Chan, PharmD, PhD

THE FDA HAS RECENTLY APPROVED ADEFOVIR DIPIVOXIL for the treatment of chronic hepatitis B infection in adults. This prodrug of adefovir is a nucleotide analog that was originally developed for the treatment of HIV infections but has also been found to be active against the hepatitis B virus. Adefovir dipivoxil is marketed as Hepsera by Gilead Sciences.

Indications

Adefovir is indicated for the treatment of chronic hepatitis B in adults with evidence of active viral replication and either evidence of persistent elevation of serum aminotransferases (ALT or AST) or histological active disease.[1]

Dosage

The recommended dose is 10 mg once daily. It may be taken without regard to meals.

Dosage reduction is recommended in patients with renal impairment and it is dosed based on creatinine clearance.[1] The dose should be 10 mg every 2 days for patients with a creatinine clearance of 20-49 mL/min, 10 mg every 3 days for creatinine clearance 10-19 mL/min, and 10 mg every 7 days for patients on hemodialysis.[1]

Potential Advantages

Adefovir appears to be effective in treating both lamivudine-resistant strains and wild type of hepatitis B virus.[1,2] A mean reduction in serum hepatitis B virus (HBV) DNA of 3.11 ± 0.94 $\log_{10}$ copies/mL were reported in 59 patients with clinical evidence of lamivudine-resistant HBV compared to no decrease in patients who remained on lamivudine alone.[1] Adefovir appears to have a low potential to be involved in drug interactions involving cytochrome P450 isoenzymes.[1]

Potential Disadvantages

Adefovir is potentially nephrotoxic. The effect appears to be dose-related and is more likely in patients who are at risk for renal dysfunction, are currently renal impaired, or are taking concomitant nephrotoxic drugs. All patients on adefovir should be monitored for changes in renal function.[1]

Exacerbations of hepatitis have been reported in up to 25% of patients who discontinue adefovir. This usually occurs within 12 weeks after discontinuation.[1] The dose of adefovir for HBV is subtherapeutic for HIV. Patients should be offered HIV antibody testing to avoid emergence of resistant HIV due to unrecognized or untreated HIV infection.[1] Lactic acidosis has been reported with the use of nucleoside analogs. Obesity, prolonged use, and female sex appear to be risk factors.[1]

Comments

The approval of adefovir for the treatment of HBV infections was based on the results of 2 double-blind, randomized, placebo-controlled studies in 507 adults. The indications were based on histological, virological, biochemical, and serological response in HbeAg positive and negative patients as well as lamivudine-resistant hepatitis B patients with either compensated or decompensated liver function.[1] In one study, 329 subjects had HBeAg-positive chronic HBV, a median total Knodell Histology Activity Index (HAI) of 10, median serum HBV of 8.38 $\log_{10}$ copies/mL, a median ALT level of 2.3 time upper limits of normal (ULN), and 24% had previous interferon alpha therapy. Histological response with adefovir was 53% at week 48 compared to 25% for placebo. Histological improvement was defined as 2 or more points decrease in the Knodell necro-inflammatory score with no worsening of the Knodell fibrosis score. Adefovir resulted in a mean reduction in HBV DNA of 3.57 ± 1.64 copies/mL compared to 0.98 ± 1.32 for placebo. The incidence of ALT normalization was 48% vs 16%, and HBeAg conversion was 12% vs 6%. The second study included 184 patients with HBeAg negative/HV DNA positive chronic HBV infection with a median total Knodell Histology Activity Index (HAI) of 10, median serum HBV of 7.08 $\log_{10}$ copies/mL, a median ALT level of 2.3 × ULN, and 41% had prior interferon alpha therapy. Histological improvement was 64% vs 35%, and mean reduction in serum HBV DNA was 3.65 ± 1.14 copies/mL compared to 1.32 ± 1.25 for placebo. ALT normalization was 72% vs 29%. Open-label studies suggest that adefovir is effective in pre- and post-liver transplant patients and those with clinical evidence of lamivudine-resistant HBV. Limited data suggest that treatment with adefovir may not lead to emergence of resistant virus after up to 60 weeks of therapy.[3] The primary limitations of adefovir therapy are nephrotoxicity and exacerbation of hepatitis upon discontinuation of therapy. Patients should be monitored periodically after discontinuation of therapy. The wholesale cost for 30 days of therapy is $440.

Clinical Implications

Chronic hepatitis B infection can be a life-long disease that can lead to cirrhosis, liver cancer, liver failure and ultimately death. The CDC estimates that about 1.25 million Americans have chronic HBV infections. Long-term control of viral replication is problematic. Current therapy includes interferon alpha-2b and lamivudine. Interferon is limited by side effects, need for parenteral administration, and toxicity in decompensated patients.[4] While lamivudine is given orally, is generally well tolerated, and can be used with hepatic decompensation, emergence of resistant strains is a major drawback—occurring in 15-32% of patients by 6 months.[4-6] Adefovir provides an oral alternative for the treatment of chronic hepatitis B infections, even if they are lamivudine-resistant. ■

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CME Questions

28. Which of the following regimens is not satisfactory for *Helicobacter pylori* eradication?

a. Bismuth, tetracycline, and metronidazole twice daily for 2 weeks.
b. Rabeprazole daily or other PPIs twice daily along with amoxicillin and clarithromycin twice daily for 1 week
c. PPI b.i.d. plus clarithromycin b.i.d. for 14 days
d. Rifabutin plus amoxicillin plus a PPI twice daily
e. Ranitidine bismuth citrate, clarithromycin, and amoxicillin or metronidazole daily for 7 days.

29. Which of the following is correct?

a. Adults with pneumococcal meningitis have been demonstrated to benefit from adjunctive corticosteroid therapy initiated when the culture results are known.
b. Adjunctive corticosteroid therapy has been demonstrated to improve outcomes in adults with meningococcal meningitis.
c. Adults with suspected bacterial meningitis should be given corticosteroids immediately before or at the same time as initiation of antibiotic therapy.

In Future Issues:

***Bartonella quintana*: What a Lousy Bug!**