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Infectious Disease [ALERT]

A monthly update of developments in infectious disease, hospital epidemiology, microbiology, infection control, emporiatrics, and HIV treatment

ABSTRACT & COMMENTARY

Otoscopic Signs of Otitis Media

By Hal B. Jenson, MD, FAAP
Dean, Western Michigan University School of Medicine, Kalamazoo, MI

Dr. Jenson reports no financial relationship to this field of study.

SYNOPSIS: In children, a bulging tympanic membrane is invariably associated with acute otitis media. Antimicrobial treatment of childhood acute otitis media should be reserved for children with this finding. Tympanic membrane abnormalities in the absence of bulging indicate otitis media with effusion.

SOURCE: Shaikh N, et al. Otoscopic signs of otitis media. *Pediatr Infect Dis J* 2011;30:822-826.

A total of 783 children 6-24 months of age were followed for an entire respiratory season by four experienced otoscopists using pneumatic otoscopy of one ear, randomly selected for each child. At each visit, the tympanic membranes were examined for color (amber, blue, gray, pink, red, white, yellow), translucency (translucent, semi-opaque, opaque), position (neutral, retracted, bulging), mobility (decreased, not decreased), and areas of marked redness as distinct from mild or moderate redness (present, absent).

In ears diagnosed with acute otitis media (AOM), the most common findings were bulging (96%), opacification (100%), white or yellow discoloration (90%), marked redness (20%), and decreased mobility (99%). Retraction was not found in ears with AOM. In ears with otitis media with effusion, the most common findings were opacification (98%), white or yellow discoloration (79%), decreased mobility (69%), and retraction (37%). In ears with no effusion the rates were, respectively, 0.5%, 0%, 0.2%, and 2%. Neither bulging nor marked redness were found in any ears diagnosed

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with otitis media with effusion, or in any ears with no effusion.

In a substudy, 135 randomly selected endoscopic tympanic membrane images from these children were evaluated by two otolaryngologists and five pediatricians from throughout the United States. These physicians had been in practice a mean of 32 years. In 51 (38%) of these 135 images, hair and/or cerumen obscured a small portion of the tympanic membrane. Colors were calibrated using an external colorimeter to ensure uniformity of color rendition on a computer monitor for each physician. In 120 of the 135 images (90%), the diagnosis made by the majority of these physicians agreed with the diagnosis by the examining otoscopists — despite the absence of any information about the patient's symptoms, the ability to assess mobility of the tympanic membrane, and partially obscured parts in 38% of images.

■ COMMENTARY

The distinction between AOM, and otitis media with effusion is a very common and important pediatric clinical issue. One of the greatest pressures on development of community antimicrobial resistance has been the high rate of antibiotic use (or overuse) for ear infections, including for otitis media with effusion where antimicrobial therapy has limited benefit.

Historically, there has been variability in the criteria used to diagnose AOM, even in clinical trials. This study shows that highly experienced clinicians rely on the presence of a bulging tympanic membrane as being pathognomonic for acute otitis media, and rarely make this diagnosis in its absence, even in the presence of other findings. In the absence of a bulging tympanic membrane, other abnormalities such as discoloration, opacification, and impaired mobility are assessed to be indicative of otitis media with effusion.

A bulging tympanic membrane is invariably the most useful physical finding for the diagnosis of childhood AOM, and antimicrobial therapy should be limited, reserved for those children with this finding. ■

ABSTRACT & COMMENTARY

Necrotizing Pneumococcal Pneumonia in Children due to *Streptococcus pneumoniae*

By Dean L. Winslow, MD, FACP, FIDSA
Chief, Division of AIDS Medicine, Santa Clara Valley Medical Center;
Clinical Professor, Stanford University School of Medicine
Dr. Winslow is a speaker for Cubist Pharmaceuticals and GSK, and is a consultant for Siemens Diagnostics.

SYNOPSIS: One hundred twelve cases of pneumococcal pneumonia were seen between 2001 and 2010 at a children's hospital in Taiwan. Bronchopleural fistula (BPF) was encountered in 18 children. Lower WBC on admission, prolonged fever, acute respiratory failure, and infection with serotype 19A were associated with BPF.

SOURCE: Hsieh YC, et al. Necrotizing pneumococcal pneumonia with bronchopleural fistula among children in Taiwan. *Pediatr Infect Dis J* 2011;30:740-744.

This study was conducted at the largest children's hospital in Taiwan. All pneumococcal isolates recovered from sterile sites from children hospitalized at this institution were maintained frozen at

-20° C since 2000. Using the hospital database and medical records, all patients < 18 years of age who were hospitalized with culture-proven pneumococcal pneumonia between 2001 and 2010 were identified. Cases were divided into: 1) pneumonia without lung necrosis and 2) necrotizing pneumonia. The latter were subdivided further into pneumonia not complicated or pneumonia complicated by BPF. Standard antimicrobial susceptibility testing was performed on isolates. Serotype was determined by Quellung reaction using antisera obtained from the Statens Serum Institut (Denmark). A subset of isolates also was examined by pulsed-field gel electrophoresis (PFGE) and multilocus sequence type using standard techniques.

During the period of study, 112 cases of culture-proven pneumococcal pneumonia were identified. Fifty-two percent of cases were complicated by empyema and 45% had necrotizing pneumonia, with 43% having both empyema and necrotizing pneumonia. Eighteen children developed BPF, all of whom had necrotizing pneumonia and empyema. Surgery was performed in 15 of 18 children with BPF and 12 children required lung resection.

The most common pneumococcal serotype seen in the 112 cases of pneumococcal pneumonia overall was type 14. From 2001 to 2010 the percentage of pneumococcal pneumonia caused by serotype 19A increased from 5% to 78%. Infection with serotype 19A was significantly associated with necrotizing pneumonia ($P = 0.005$) and with development of BPF ($P = 0.02$). All 12 isolates of type 19A pneumococcus belonged to multilocus sequence type clonal complex (CC) 320.

Pathology data available for the 12 children who underwent surgical resection showed suppurative necrosis and abscess formation in 75% and coagulation necrosis was seen in 92% of cases.

■ COMMENTARY

This study showed that *Streptococcus pneumoniae* serotype 19A CC320 was strongly associated with necrotizing pneumococcal pneumonia and development of BPF. The increased frequency of isolation of this pathogen over the 10 years of the study is almost certainly related to two factors: the replacement of serotypes, including in the PCV7 vaccine, by non-vaccine serotypes and possibly antibiotic selection since an increased frequency of isolation of serotype 19A also has been seen in countries where use of PCV7 has been low.

In addition to causing necrotizing pneumonia, type 19A has become a predominant cause of other invasive pneumococcal disease syndromes, including empyema, mastoiditis, and hemolytic uremic syndrome. This study is interesting since it reported a comprehensive experience with invasive pneumococcal disease in children over a 10-year period and included pathology data. The common finding of pulmonary infarction in resected lung tissue in addition to abscess formation is striking and suggests that this pathogen contributed to arteritis and vascular thrombosis. Clearly, serotype 19A pneumococcus is a formidable pathogen (and seems to me to have some parallels to *S. milleri* group organisms). Further research to understand the pathogenicity of this organism, as well as host-pathogen relationships, would seem to be a fruitful area of study. ■

ABSTRACT & COMMENTARY

Effect of an Oxazolidinone and Clindamycin on *Staphylococcus aureus* Virulence Factors

By Dean L. Winslow, MD, FACP, FIDSA

SYNOPSIS: In *Staphylococcus aureus* strains isolated from patients with complicated skin and skin structure (CSSI) infections generally produced high levels of phenol-soluble alpha-type (PSMa) peptides. TR-700 (an oxazolidinone) and clindamycin inhibited phenol-soluble modulin production at a concentration one-half the MIC of the organism, but exhibited weak to modest induction at one-quarter to one-eighth the MIC in some isolates.

SOURCE: Yamaki J, et al. Antivirulence potential of TR-700 and clindamycin on clinical isolates of *Staphylococcus aureus* producing phenol-soluble modulins. *Antimicrob Agents Chemother* 2011;55: 4432-4435.

Baseline production of PSMa subtypes was examined in 50 PVL-positive methicillin-susceptible *Staphylococcus aureus* (MSSA) and MRSA clinical isolates using liquid chromatography-tandem mass spectrometry (LC-MS-MS), and these results were compared

to a control strain, LAC (USA300). MICs were determined using a broth macrodilution method. MIC 50/90 values for TR-700 and clindamycin were 0.25/0.375 µg/mL and 0.125/0.188 µg/mL, respectively. Supernatants were harvested after incubation with study drug at one-half, one-quarter, and one-eighth MICs for PSM quantitation by LC-MS-MS and global regulator (agrA and RNAIII) expression by reverse transcription-PCR (RT-PCR). PSMa production at baseline varied significantly between isolates, but did not differ by methicillin resistance, type of CSSI (cellulitis or abscess), or size of abscess.

Of the 21 isolates selected for testing vs. the two antibiotics, TR-700 at one-half MIC inhibited PSM production in a dose-dependent fashion with PSMa3 being most inhibited. Paradoxical induction of PSMa by TR-700 was observed at one-quarter and one-eighth MIC, primarily in strains with low baseline production of PSMa3. Clindamycin had a stronger inhibitory effect on overall PSM production vs. TR-700 in seven isolates and completely abolished PSMa3 production in five of seven isolates. Similar to TR-700, PSM production was weakly induced at one-quarter and one-eighth MIC in two isolates and the LAC strain control.

■ COMMENTARY

While this is an in vitro study, the results are interesting from a mechanistic standpoint and are potentially relevant to clinical practice. Secreted exotoxins, including toxic shock syndrome toxin 1 (TSST-1), a-hemolysin (Hla), and Panton-Valentine leukocidin (PVL) have been shown to contribute to the virulence of both MSSA and MRSA. The PSMa peptides have more recently been described as important virulence factors implicated in pathogenesis of CSSIs, bacteremia, and pneumonia. Like PVL, PSMa peptides cause pore formation in neutrophils and release of inflammatory mediators. PSMa peptides are secreted as both formylated and nonformylated forms and the formylated forms display greater cytotoxicity. PVL, Hla, and the PSMs are under control of agrA and RNAIII of the agr system.

In an important paper published several years ago, Stevens et al elegantly demonstrated the impact of protein-synthesis inhibiting antibiotics on expression of exotoxin genes in *S. aureus*.[1] In addition, there exists moderately strong clinical evidence to support the use of antibiotics such as clindamycin and the oxazolidinone, linezolid, in vivo to reduce toxin production and improve clinical outcomes. This paper by Yamaki et al extends these findings by demonstrating the inhibitory effect of an oxazolidinone and clindamycin on what may be the most important *S. aureus* virulence factor, PSMa. In addition, the demonstration that significantly sub-inhibitory concentrations of both the oxazolidinone and clindamycin may induce toxin production by some strains of *S. aureus* suggests that underdosing of these drugs should be avoided. ■

Reference

1. Stevens DL, et al. Impact of antibiotics on expression of virulence-associated exotoxin genes in methicillin-sensitive and methicillin-resistant *Staphylococcus aureus*. *J Infect Dis* 2007;195: 202-211.

ABSTRACT & COMMENTARY

Movies and Politicians: Which Are Reality-based?

By Stan Deresinski, MD, FACP, FIDSA

Hollywood movies have always created their own reality. Meanwhile, the rest of us slog through the conventional reality of our daily lives. Many of us may have assumed that our politicians live in the same world we do and that they have similar perceptions of it — a view that has definitively and repeatedly been demonstrated to be foolish and naïve. Parallel examinations of a new popular movie and the statements of a candidate for her party's nomination for president have demonstrated a reversal — reality from Hollywood and a startling rejection of reality by a prominent politician.

Steven Soderbergh's movie "Contagion" begins with Gwyneth Paltrow becoming ill, developing seizures, and dying within days of encephalitis. She proves to be "Patient Zero" of a worldwide

epidemic caused by a previously unknown infection with an associated mortality rate in excess of 20% that results in the deaths of millions. This extraordinary mortality leads to the necessity of using mass graves and the emergence of progressively escalating social disorder, exacerbated by rumor-mongering and false promises of a cure. Meanwhile, public health workers at the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC) struggle to understand the epidemic's origin and means of spread while, at the same time, instituting preventive actions.

CDC scientists set out to determine the etiology of the infection and to develop a protective vaccine. They determine the cause to be a virus that appears to have been modeled upon a known zoonotic cause of encephalitis, the Nipah virus. Epidemiologic investigation eventually finds that uprooting a forest of palm trees to establish a new piggery disrupted a colony of frugivorous bats. An infected bat regurgitates the indigestible portions of a banana that is then eaten by a pig. The pig finds its way to the kitchen of a Macao casino where it is prepared by a chef who ends up shaking his unwashed hands with a character played by Gwyneth Paltrow. Shortly after, Ms. Paltrow's character flies home to Minneapolis to her child and her husband (Matt Damon). Like Ms. Paltrow's character, the child dies, but Matt Damon survives. The epidemic progresses throughout the world as the CDC and WHO struggle to solve the problem. Eventually a vaccine is developed and distributed, but not before millions of deaths, including that of a CDC Epidemiologic Investigation Service Officer (Kate Winslett).

The movie is amazingly realistic in many aspects, including much of its science. The major liberty it takes, clearly for dramatic effect, is time compression. The initial spread of the virus is remarkably fast, probably unrealistically so. In addition, 57 versions of the vaccine are tested in primates before an effective one is developed. The vaccine undergoes unspecified further testing, is manufactured and distributed — all within a few months. This remarkable celerity may prove feasible at some time in the future, but not yet.

The mutated virus causing the epidemic, called MEV-1 (it is unstated, but perhaps standing for "meningoencephalitis virus-1") is clearly modeled on the Nipah virus, which was first identified in Malaysia in 1988-1999 and whose natural host is a flying fox, a type of frugivorous bat. Nipah outbreaks in Asia have been associated with contact with pigs, but also with human-to-human transmission and with eating contaminated fruit and fruit juices, such as raw date palm juice. Clinical illness starts with influenza-like symptoms with, in some cases, progression to pneumonia and to encephalitis, often ushered in by seizures with progression to coma in 24-48 hours. There is no known effective treatment and no vaccine is available.

So much for reflections of reality. A member of the previous presidential administration (said to be Karl Rove, former Deputy Chief of Staff and Senior Advisor to President George W. Bush) was quoted as scoffing at the "reality-based community," indicating that he and his colleagues were creating their own truth. And more recently, while Hollywood was doing its best at being realistic, Representative Michelle Bachman (R-Minn) was joining the attack on the "reality-based community."

The reality: Human papillomavirus (HPV) causes, among other malignancies, most of the more than 200,000 cervical cancers that occur in the world each year, most in developing countries where screening is not routinely performed. In the United States, where Pap screening is the rule, there are, nonetheless, 12,000 cases and 4,000 deaths each year. An effective preventive vaccine has been available for several years and is recommended for administration to girls beginning at age 11 years (and as early as age 9 years) — ideally before sexual debut, since HPV is the most prevalent sexually transmitted infection in the United States and the vaccine does not protect against existing infection. The quadrivalent vaccine also protects against genital warts and recently received approved for use in males as young as 9 years of age. Importantly, the vaccine, which does not contain live virus, has an impressive safety record.[1]

Despite this safety record, Rep. Bachman, a graduate of the Oral Roberts School of Law, in a recent Republican candidates' debate, called the vaccine "dangerous" and spoke of the "poor innocent little girls" upon whom it was inflicted. The following day she went on to relay an unsubstantiated story about a girl who "became mentally retarded" after receiving the vaccine. Associated statements by her and some of her fellow candidates also contained the implication that any public health mandate constituted an unconstitutional denial of freedom. As an apparently charter member of the seemingly expanding cult of "denialism" — the rejection

of science and its methods and of objective reality itself — perhaps these statements should have been expected. They, nonetheless, have the potential to cause enormous damage by causing individuals to reject the vaccine for themselves or their children. Will the denialists take responsibility for the resultant deaths? ■

Reference

1. Gee J, et al. Monitoring the safety of quadrivalent human papillomavirus vaccine: Findings from the Vaccine Safety Datalink. *Vaccine* 2011 Sep 9; Epub ahead of print.

ABSTRACT & COMMENTARY

Clostridium difficile BI: From Canada to the Second City

By Joseph F. John, MD, FACP, FIDSA, FSHEA

Associate Chief of Staff for Education, Ralph H. Johnson Veterans Administration Medical Center; Professor of Medicine, Medical University of South Carolina, Charleston

Dr. John reports no financial relationship to this field of study.

SYNOPSIS: Severe disease was common and crude mortality was considerable among patients diagnosed with *Clostridium difficile* in Chicago in February of 2009. The BI strain was the predominant strain identified (61%).

SOURCE: Black SR, et al. *Clostridium difficile* outbreak strain B1 is highly endemic in Chicago area hospitals. *Infect Control Hosp Epidemiol* 2011;32:897-902.

A 1-month prevalence study was done in 2009 at 25 of the 56 contributing hospitals participating in the Chicago Health Alert Network. Patients were considered having *Clostridium difficile* infection (CDI) if they had three or more watery stools and a positive *C. difficile* toxin or pseudomembranous colitis. Severe CDI was defined as having CDI requiring ICU care. Rates were calculated per 10,000 patient-days during the month of February, 2009. Stool samples were collected and cultured. *C. difficile* isolates were characterized for HindIII restriction endonuclease analysis (7 groups). Note that only hospital onset cases were included in the study.

Of the 56 network hospitals, 25 contributed data and samples to this study. There were 263 incident episodes and, of these, 16% were considered severe and 57% were females. Twenty patients died, so the crude mortality rate was 8%. Thirty-seven percent of the patients had to extend care at a long-term care facility where the average length of stay (LOS) was 7 days.

Restriction enzyme analysis found that the majority were BI (61%), followed by J, G, BK, CF, Dh, or K. There were 22% non-epidemic groups that were not further characterized. BI was present in hospital and community origin organisms. BI patients had a high likelihood (50%) of needing long-term care and 18% of the BI patients had severe outcomes. Note that BI was very widespread, occurring at 18 of the 20 health care facilities.

■ COMMENTARY

Hats off to the wonderful consortium of hospitals constructed in the Chicago Health Alert Network. Managing to organize 25 organizations of any kind in a large U.S. city is a great accomplishment, including the submission of 129 specimens that yielded a cultured organism. The major point of this study is that a highly virulent strain that originated in Canada[1] — one that has come to be known as the B1 strain — has infiltrated the lower 48 and, in at least one major city, it has become endemic, causes community as well as hospital disease, and can be fatal in up to 8% of episodes.

Can we do anything to control the spread of such a virulent enteropathogen? America knows how to build reporting networks. Reported on PBS *Frontline*, Sept. 6, 2011, there are a series of highly secret, yet very functional, antiterrorist nodes throughout the country. Assuming these nodes have been effective in thwarting terror events, perhaps they provide models better than ones we have built to alter the occurrence and spread of specific events. Perhaps a city like Chicago could enhance its efforts to limit spread of virulent pathogens. The authors do emphasize that one outgrowth of the current study is the

need for close communication between acute care facilities.

The notorious B1 strain, as discovered in this intriguing study, was prominent throughout Chicago hospitals in 2009. Why did the strain delay its entry into the heartland, yet predominate when it did? Answers to the first part of the question remain without explanation. As for the second question, there is likely some colonization advantage for this strain, once introduced, that showed vicious virulence during its Canadian phase, enough that hospitals had to be closed. From the data in this article, it is clear that B1 has spread into the heartland of North America. With the leadership of this hospital consortium, Chicago has given us a model to allow cities to have early alerts and to cooperate in assembling a holistic molecular epidemiology of pathogen spread. ■

Reference

1. Pepin J, et al. *Clostridium difficile*-associated diarrhea in a region of Quebec from 1991 to 2003: A changing pattern of disease severity. *CMAJ* 2004;17:466-472.

ABSTRACT & COMMENTARY

HIV-1 Protein, Nef, Contributes to Insulin Resistance

By Dean L. Winslow, MD, FACP, FIDSA

SYNOPSIS: The HIV-1 regulatory protein, Nef, was shown in cell cultures of adipocytes to cause reduced glucose uptake, inhibition of glucose transporter protein 4 (GLUT 4), decreased phosphorylation of signal transducing proteins, and alteration in cortical actin organization.

SOURCE: Cheney L, et al. Nef inhibits glucose uptake in adipocytes and contributes to insulin resistance in human immunodeficiency virus type 1 infection. *J Infect Dis* 2011;203:1824-1831.

3T3L1 pre-adipocytes in cell culture were treated overnight with myristoylated or non-myristoylated recombinant Nef. Glucose uptake was measured with and without insulin stimulation. Adipocytes transfected with a Myc-GLUT4-green fluorescent protein (GFP) were studied after treatment with Nef with or without insulin stimulation. Actin polymerization was studied using rhodamine-stained cells. Immunoblot analysis of phosphorylation of signal transduction proteins Akt and AS160 was performed.

Nef was shown to inhibit insulin-stimulated glucose uptake in a dose-dependent manner. Nef also inhibited GLUT4 fusion with the plasma membrane in insulin-stimulated adipocytes. Finally, Nef was shown to alter the proximal signal transduction pathway of insulin and to disrupt F-Actin at the cortical actin ring.

■ COMMENTARY

While a number of antiretroviral agents have been implicated in contributing to both insulin resistance and lipid abnormalities, HIV also directly causes metabolic disturbances. Nef, a 27 kDa nonstructural protein essential for replication and evasion of host responses, is one of several regulatory proteins encoded by HIV-1 and modulates a number of cellular processes by protein-protein interactions. Nef has been shown to down-regulate CD4 and MHC1 molecules, alter signal transduction pathways, interact with the actin cytoskeleton, and affect actin polymerization. These processes are important for insulin action and glucose homeostasis. Nef is secreted into the extracellular compartment and can be measured in plasma. Insulin resistance is found in ARV-naïve patients, and HIV viral load is a predictor of metabolic syndrome.[1]

This in vitro study presents a nice demonstration of what is most likely a clinically relevant mechanism contributing to the problem of insulin resistance with resultant Type 2 diabetes and dyslipidemia so commonly seen in HIV-infected patients. ■

References

1. Squillace N, et al. Detectable HIV viral load is associated with metabolic syndrome. *J Acquir Immune Defic Syndr* 2009;52: 459-464.

ABSTRACT & COMMENTARY

Moxifloxacin for Odontogenic Infection

By Dean L. Winslow, MD, FACP, FIDSA

SYNOPSIS: In a randomized, double-blind clinical trial, treatment with moxifloxacin was as effective as clindamycin in the treatment of dental abscess and superior to clindamycin in the treatment of odontogenic inflammatory infiltrates.

SOURCE: Cachovan G, et al. Comparative efficacy and safety of moxifloxacin and clindamycin in the treatment of odontogenic abscesses and inflammatory infiltrates: A phase II, double-blind, randomized trial. *Antimicrob Agents Chemother* 2011;55:1142-1147.

Outpatients with a diagnosis of either dentoalveolar or periodontal abscess or a diagnosis of gingival inflammatory infiltrates were randomized to receive either moxifloxacin 400 mg daily or clindamycin 300 mg QID, both for 5 days, in a prospective, randomized, placebo-controlled, double-dummy clinical trial design. The primary efficacy endpoint was percent reduction in pain on a visual analogue scale (VAS) at days 2-3 from baseline. (This endpoint has been shown historically to be a useful endpoint for dental intervention studies.)

Among gingival infiltrate patients, the 21 patients randomized to moxifloxacin (MXF) experienced a 61% median reduction in pain at days 2-3 vs. 23% in the 19 patients receiving clindamycin (CLI) ($P = 0.006$). Among abscess patients, the 15 patients receiving MXF had a 56% reduction in pain vs. 43% in the 16 patients receiving CLI ($P = 0.358$). Objective evidence of infiltrate and abscess resolution by day 5-7 of treatment also favored MXF.

While not reaching statistical significance, MXF appeared to be better tolerated than CLI with lower incidence of diarrhea and nausea (1 in the MXF arm vs. 8 in the CLI arm).

■ COMMENTARY

Clindamycin is commonly prescribed for treatment of odontogenic infection in both the inpatient and outpatient setting. While generally effective, clindamycin requires TID or QID dosing and is commonly associated with diarrhea (including *Clostridium difficile* colitis). Moxifloxacin, while also occasionally associated with *C. difficile* disease, is generally well-tolerated, has the advantage of once daily dosing, and has in vitro activity against most of the pathogens implicated in odontogenic infections.

This study nicely demonstrates that MXF is superior to CLI for treatment of dental inflammatory infiltrates and at least equal to CLI as adjunctive treatment of odontogenic abscess. MXF appeared to have fewer side effects than CLI. ■

ABSTRACT & COMMENTARY

Intravenous Immune Globulin for Neonatal Sepsis

By Hal B. Jenson, MD, FAAP

SYNOPSIS: Intravenous immune globulin for suspected or proven severe neonatal infection had no effect on clinical outcomes including subsequent sepsis, death, or major or non-major disability at 2 years of age.

SOURCE: The INIS Collaborative Group. Treatment of neonatal sepsis with intravenous immune globulin. *N Engl J Med* 2011;365:1201-1211.

A double-blind, randomized, controlled trial conducted by the International Neonatal Immunotherapy Study (INIS) compared adjunctive therapy of human nonspecific polyvalent IgG intravenous immune globulin to placebo in the treatment of newborn infants with suspected or proven sepsis who were also receiving antibiotic therapy. Newborns receiving antibiotics and having birth weight less than 1500 g, requiring assisted ventilation, or with

evidence of infection of a usually sterile body site were randomized to receive intravenous immune globulin (500 mg/kg, 2 doses 48 hours apart) or an identical volume of placebo. Primary outcomes were death or major disability at 2 years of age, including cognitive function using the Parent Report of Children's Abilities-Revised (PARCA-R).

From 2001 to 2007, 3,493 infants were recruited from 113 hospitals in nine countries. Newborn and maternal characteristics were very similar. Outcomes at 2 years of age were available for 97% of surviving infants. In the group receiving intravenous immune globulin, 686 of 1,759 infants (39.0%) either died or had major disability at 2 years of age, compared with 677 of 1,734 infants (39.0%) in the placebo group. There were no significant outcome differences for any secondary outcome, including rates of subsequent episodes of sepsis and by causative organisms. There were 22 adverse events reported with 12 in the group receiving intravenous immune globulin (including 2 deaths) and 10 in the placebo group (including 4 deaths).

■ COMMENTARY

There are more than 20 reported trials involving more than 5,000 preterm infants studying the use of polyvalent IgG to treat suspected or proven sepsis in preterm infants. Relatively low numbers of enrollees, small differences in treatment groups, conflicting results even among meta-analyses, and variable scientific quality of many reports have resulted in uncertainty of the value of intravenous immune globulin as adjunctive therapy for neonatal sepsis.

This study is notable for the double-blind and randomized study design with a large number of enrolled infants (3,493), and measurements of both short-term mortality and long-term (at age 2 years) disability outcomes. Based on this trial, intravenous immune globulin has no effect on the outcomes of suspected or proven neonatal sepsis. ■

CME INSTRUCTIONS

To earn credit for this activity, please follow these instructions:
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CME QUESTIONS

1. Which of the following otoscopic findings it the most accurate single indicator of the presence of acute otitis media?

a. Tympanic membrane retraction
b. Marked tympanic membrane redness
c. Bulging tympanic membrane
d. Amber color

2. Which of the following is *correct* with regard to the treatment of odontogenic infection?

a. Moxifloxacin was statistically superior to clindamycin in pain reduction in patients with dental abscesses.
b. Moxifloxacin was statistically superior to clindamycin in pain reduction in patients with infiltrative gingival infection.
c. Clindamycin was better tolerated than moxifloxacin.
d. Clindamycin is dosed less frequently each day than is moxifloxacin.

3. Which of the following is correct with regard to the treatment of neonatal sepsis?

a. IVIG without antibiotics is as effective as IVIG with antibiotics.
b. IVIG with antibiotics is superior to IVIG without antibiotics.
c. IVIG is superior to antibiotics alone.
d. IVIG with antibiotics is no more effective than antibiotics alone.

CME OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- discuss the diagnosis and treatment of infectious diseases;
- explain current data regarding the use of new antibiotics for commonly diagnosed diseases and new uses for traditional drugs;
- discuss the latest information regarding risks, benefits, and cost-effectiveness of new and traditional diagnostic tests; and
- discuss new information regarding how infectious diseases are transmitted and how such information can lead to the development of new therapies.

Updates

By Carol A. Kemper, MD, FACP

Prison brew

Source: ProMED-mail post 2011 Oct 10; Available at: www.promedmail.org.

In early October, 12 inmates from the Utah State Correctional Facility became acutely ill with nausea, vomiting, facial paralysis, and visual blurring.

All 12 were diagnosed with acute botulism, 8 of whom required hospitalization and botulism anti-toxin. Three remain hospitalized, requiring ventilatory support. Four others were well enough to be cared for as outpatients.

The culprit is believed to be the ingestion of jail house home-brewed liquor, which the men reportedly concocted out of potatoes, oranges, apples, and pineapples salvaged from their meals. Originally called "pruno" because a common ingredient was breakfast prunes, similar jail house concoctions go by a variety of names including juice, jump, hooch, and raisin jack. It can be "brewed" from such simple ingredients as cake frosting, bread, jelly, and milk. A proven recipe found on the web includes a Ziploc bag (or heavy duty garbage bag and rubber bands), 9 peeled oranges, an 18 oz can of fruit cocktail, 50 sugar cubes, 6 tsp of ketchup, and water — fermentation begins within 48 hours and the slop can be drunk within 9 days. Adding dinner rolls (with yeast) can cut the fermentation time in half. One taste-tester described the concoction as like drinking "thunderbird thru a dumpster of rotten garbage," which is a testament to how badly some inmates want to get drunk.

To keep the bag from exploding, it must be opened to let out the gases, maintaining an anaerobic environment, which is perfect for botulism toxin production. The use of potatoes may increase the risk of botulism. Similar outbreaks of jail house-brewed botulism occurred in 2004 and 2005 in prisons in Riverside and Monterey, Calif. ■

Transfusion-associated babesiosis in the United States

Source: Herwaldt BL, et al. Transfusion-associated babesiosis in the United States: A description of cases. *Ann Intern Med* 2011 Sep 5; Epub ahead of print.

Transfusion-associated babesiosis is an uncommon, poorly recognized, but serious complication that may be on the increase in the United States. These authors summarized all 159 recognized cases occurring between 1979-2009 in the United States. While babesiosis was not considered a reportable disease for many years, the authors went to great lengths to track down all known cases of transfusion-associated infection. Positive donors were identified in 136 (86%) of cases. All but four cases were associated with transfusion of red cell components. The cases occurred throughout the year and were reported from 19 states, although 87% of the cases occurred in just seven states: Connecticut, Massachusetts, New Jersey, New York, Rhode Island, Minnesota, and Wisconsin. While cases were reported from states other than these, many of these donors had visited or resided in states known to be endemic for the organism. Three cases of *B. duncani* infection were reported in 2004 and 2008 from California and Washington.

The median age of transfusion-related *B. microti* cases was 65 years (range, < 1 to 94 years). Most of the patients were either very young (18 were infants, 13 of whom were cluster-associated) or very old. However, a subset of about 25 patients were in the middle age group, 19 of whom had hereditary blood disorders, such as sickle cell anemia or transfusion-dependent thalessemia, and/or splenectomy. The all-cause mortality rate was 19%, although many patients were critically ill for other reasons.

During the period of study, only 7 (4%) cases occurred between 1979 and 1989, whereas 122 (77%) occurred between 2000 and 2009. These data suggest that either post-transfusion babesiosis may be occurring with increasing frequency or it is increasingly being recognized and reported. The authors report that many of the cases were only incidentally recognized. Many of the cases were detected by the laboratory during routine manual examination of a peripheral blood smear, and several cases were detected post-mortem. Several of the cases were misdiagnosed, as demonstrated by the fact that 14 of 20 cases were ring forms and initially received anti-malarial treatment. The authors argue that babesiosis should be considered in the differential of fever of unknown origin fol-

lowing transfusion, or any case of post-transfusion hemolysis with or without fever. ■

Increasing alarm over NDM-resistance

Source: ProMED-mail post 2011 Oct 5; Available at: www.promedmail.org.

Last year, *Morbidity Mortality Weekly Report* described the emergence of a novel resistance mechanism, called New Dehli metallo-beta-lactamase (NDM-1), which had been identified in three *Enterobacteriaceae* isolates in the United States between January and June 2010.[1] The three isolates, including an *Escherichia coli*, *Klebsiella pneumoniae*, and *Enterobacter cloacae*, all carried "blaNDM-1," which confers resistance to all beta-lactams and carbapenems, with the exception of aztreonam. These three isolates were, however, additionally resistant to aztreonam, presumably by an additional resistance mechanism. The organisms were isolated from 3 patients who received recent medical care in India. Similar isolates are being reported with increasing frequency in the United Kingdom, as well as Western Europe and Canada, generally in persons who have received recent medical care in India and Pakistan.

Since that report, alarm at the increase in these highly drug-resistant organisms in India, and their spread to the West, has prompted India to call for a global summit on antibacterial resistance. NDM and other drug-resistant mechanisms are contributing to an increased mortality in India, especially in infants. A West Bengal hospital recently described the deaths of 4 infants from these organisms. Drug resistance may contribute to at least 30% of the 190,000 annual infant deaths in India — either because of lack of access to antibiotics to which the bacterium is sensitive or due to extremely drug-resistant bacteria for which there is no treatment. Data from a well-known tertiary care hospital in New Dehli suggest that of 10,899 culture specimens collected in a 5-month period, more than 2,500 specimens from the ICU and 2,700 from the general ward yielded organisms containing NDM-resistance (usually patients with *E. coli* infection or pneumonia). ■

Reference

1. CDC. Detection of *Enterobacteriaceae* isolates carrying metallo-beta-lactamase — United States, 2010. *MMWR Morb Mortal Wkly Rep* 2010;59:750.

Pedicure-associated furunculosis

Source: Stout JE, et al. Pedicure-associated rapidly growing mycobacterial infection: An endemic disease. *Clin Infect Dis* 2011;53: 787-792.

Rapidly growing mycobacteria (RGM) have been increasingly identified with skin and soft-tissue infection, especially those associated with pedicures at nail salons. An outbreak of 110 pedicure-associated furunculosis cases (specifically due to *Mycobacterium fortuitum*) occurred in our area in 2000. I provided care for about a dozen "victims" when a second, larger outbreak involving 140 customers and 33 different salons occurred in our county in 2004. This second outbreak involved multiple different RGMs, including *M. fortuitum* and *M. chelonae/asbscessus*. One immunocompromised patient died of her infection. These can be difficult infections to diagnosis and treat, cultures are often negative, even when tissue cultures are obtained, and treatment frequently requires the administration of two or more antimycobacterial agents for months at a time. Patients are often left with residual scars.

Both of these outbreaks quietly ended just as mysteriously as they began. Interestingly, adjacent San Mateo County was not involved — only salons in Santa Clara County. Although the new-fangled whirlpool salon chairs were considered a suspect source, extensive evaluation of a number of implicated salons and chairs failed to demonstrate a consistent source. That investigation did reveal that extensive biofilm, matted hair, and debris can build up within the whirlpool pipes, couplings, and valves of the chairs, and recommendations were made for routine cleaning, using disinfectant and bleach.

A similar outbreak of 40 cases of pedicure-associated furunculosis occurred in two counties in North Carolina from 2005 to 2008, 55% of which were due to ***M. abscessus/chelonae*** group organisms. Again, extensive investigation failed to reveal a specific source. Although a number of RGM were recovered from tap water, footbaths, and biofilm samples from 11 of 13 implicated salons and 4 of 11 controls salons (P = 0.032), no specific relationship could be identified between specific salons and specific organisms. Nonetheless, the authors concluded that the heated whirlpool waterbaths are a likely source. Because many nail salons form "co-ops" and share supplies, some of which are imported, and given the local nature of these outbreaks, I have been suspicious that a contaminated lotion or nail product might be the culprit. Avoiding shaving your legs one to two days before getting a pedicure may decrease the risk of infection. ■

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[IN FUTURE ISSUES]

Syphilis screening with the treponemal immunoassay

Transfusion-associated babesiosis

PHARMACOLOGY WATCH

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

Medication Poisonings Are Increasing in Children

In this issue: Medication poisonings in children; rosuvastatin vs atorvastatin for atherosclerosis; saw palmetto for prostate symptoms; using atypical antipsychotics for off-label indications in adults; and FDA actions.

More medications, more poisonings

Medication poisonings among young children have increased in frequency in recent years despite safety measures to prevent them, according to a new study from *Pediatrics*. Researchers used patient records of more than 450,000 children 5 years old or younger from 2001-2008. The rate of poisoning increased by about a third during this time span compared to the prior decade. Child self-exposure was responsible 95% of the time with ingestion of prescription drugs causing more than half of the poisonings and more than 70% of significant injuries. The most dangerous drugs were opioids, sedative-hypnotics, and cardiovascular agents. The authors conclude that the number of children visiting emergency departments after medication exposure is increasing, with the majority of ingestions caused by children finding and ingesting medications by themselves. They suggest that efforts at poison-proofing homes with young children "may be a good, but insufficient, strategy." They further suggest that the increase in poisonings is in part due to the rise in number of medications in the environments of young children, with the number of adults taking medications, especially opioid medications, rising dramatically in the last 10 years. Other possible explanations include more siblings on medications, especially ADHD meds, as well as exposure to grandparents' homes where child-proofing may not be as rigorous. They further conclude that current preventive efforts are inadequate and new measures, such as efforts targeting home medication safety (including storage of medications and child-resistant closures) and repackaging (such as blister packs and flow restrictors on liquid medications), should be considered. (*Pediatrics* published online September 16, 2011.) ■

Rosuvastatin no better than atorvastatin

Rosuvastatin is no better than atorvastatin in slowing progression of coronary atheroma, according to AstraZeneca, the manufacturer of rosuvastatin and sponsor of the study. Researchers compared rosuvastatin 40 mg to atorvastatin 80 mg in the Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin vs Atorvastatin (SATURN) trial. The primary efficacy endpoint was change from baseline in percent atheroma volume in a targeted coronary artery as assessed by intravascular ultrasound. After 104 weeks of treatment in some 1300 patients, there was a numerical greater reduction in favor of rosuvastatin, but the reduction did not reach statistical significance (astrazeneca.com/Media/Press-releases). The full results will be presented at the American Heart Association meeting in

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5404. E-mail: neill.kimball@ahcmedia.com.

November. The results come as a blow to the manufacturer of rosuvastatin (Crestor) who had hoped to gain a marketing advantage before the introduction of low-cost generic atorvastatin into the market, slated for December. ■

Saw palmetto for prostate symptoms

Saw palmetto is ineffective for treating lower urinary tract symptoms (LUTS) in men with benign prostatic hyperplasia (BPH), even at higher doses, according to a new study. Previous studies have shown no benefit from saw palmetto, but researchers in this current study set out to test the efficacy of 2-3 times the normal daily dose on men over the age of 45 with significant LUTS. The main outcome was the difference in American Urologic Association Symptom Index score between baseline and week 72. Both saw palmetto and placebo led to an improvement in symptoms with a favorability toward placebo regardless of the dose of saw palmetto. Doses tested were a single 320 mg tablet per day with dose escalation to 2, then 3, tablets per day. The authors conclude that increasing doses of saw palmetto root extract did not lower LUTS more than placebo in men with BPH (*JAMA* 2011;306:1344-1351). This is the second rigorously controlled trial after the Saw Palmetto Treatment for Enlarged Prostates study (*N Engl J Med* 2006;354:557-566) to show no benefit from the supplement on LUTS in men with BPH. ■

Off-label use of atypical antipsychotics

Controversy surrounds the use of atypical antipsychotics for off-label indications in adults, especially the elderly with dementia. A new meta-analysis reviews the evidence of efficacy of these drugs for various off-label uses. Of more than 12,000 studies considered, 162 were included in the analysis. Drugs reviewed included risperidone (Risperdal), olanzapine (Zyprexa), quetiapine (Seroquel), aripiprazole (Abilify), ziprasidone (Geodon), asenapine (Saphris), iloperidone (Fanapt), and paliperidone (Invega). For elderly patients with dementia, a small but statistically significant improvement in symptoms such as psychosis, mood alterations, and aggression were seen with aripiprazole, olanzapine, and risperidone. For generalized anxiety disorder, quetiapine was the most effective, while for obsessive-compulsive disorder, risperidone was associated with a 3.9 greater likelihood of favorable response, compared with placebo when used with antidepressants. There was no benefit seen with any of the drugs used in treating eating disorders, substance abuse, or insomnia, and only marginal benefit in personality disorders or posttraumatic stress disorder. All of these drugs have a boxed warning regarding increased mortality in elderly patients with dementia and increased risk of suicidality. Increased risk of death was seen in elderly patients with a number needed to harm (NNH) of 87. Also noted was increased risk of stroke, especially with risperidone (NNH = 53), extraparametal symptoms (NNH = 10 for olanzepine, NNH = 20 for risperidone), and urinary tract symptoms (NNH range = 16-36). Weight gain was also a problem in non-elderly adults, particularly with olanzapine (incidence of more than 40%), while akathisia was more common with aripiprazole. Other common side effects included fatigue, sedation, and extrapyramidal symptoms. (*JAMA* 2011;306:1359-1369). ■

FDA actions

The FDA has issued a warning regarding the potential for arrhythmia associated with the antinausea drug ondansetron (Zofran). The drug should be avoided in patients with QT prolongation as they are at particular risk of developing torsade de pointes. Ondansetron should be used with caution in patients with congestive heart failure, bradyarrhythmias, those predisposed to low potassium or magnesium, and in those taking drugs that cause QT prolongation. These patients should have electrocardiogram monitoring if ondansetron is indicated. The FDA is requiring new labeling changes to reflect these warnings.

The FDA is reminding physicians and patients that epinephrine inhaler (Primatene Mist), the only over-the-counter inhaler for asthma, will be removed from the market on December 31. The withdrawal is due to an international ban on chlorofluorocarbon propellant. The FDA is recommending that physicians ask their patients with asthma if they use Primatene Mist and talk to them about prescription alternatives.

The FDA has approved infliximab (Remicade) to treat moderate-to-severe ulcerative colitis (UC) in children 6 years and older who have had inadequate response to conventional therapy. The drug is already approved for adults with UC. The approval was based on a randomized, open-label trial of 60 children ages 6 to 17 with moderate-to-severe UC. The drug carries a boxed warning for serious infections and cancer. Infliximab is manufactured by Janssen Biotech. ■