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Incisive Commentary and Clinical Abstracts on Current Issues in Infectious Diseases

ABSTRACT & COMMENTARY

Varicella Zoster Virus and Granulomatous Arteritis

By Dean L. Winslow, MD, FACP, FIDSA

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Dr. Winslow reports no financial relationships relevant to this field of study.

SYNOPSIS: Varicella zoster virus antigen was identified in 11 of 11 aortas with pathologically verified granulomatous arteritis and in only five of 18 control aortas from surgical or autopsy specimens.

SOURCE: Gilden D, White T, Boyer PJ, et al. Varicella zoster virus infection in granulomatous arteritis of the aorta. *J Infect Dis* 2016;213:1866-1871.

Researchers examined surgical pathology databases at Massachusetts General Hospital from 1990 to present and identified 11 cases that met criteria for granulomatous arteritis of the aorta. The cases included five men and six women who ranged from 32-87 years of age. Eighteen control aortas were studied and included specimens from eight men and 10 women ranging from 23-66 years of age. No control aortas had evidence of inflammation or giant cell arteritis (GCA). Formalin-fixed tissue blocks were examined for varicella zoster virus (VZV) by immunohistochemistry and polymerase chain reaction (PCR).

Immunohistochemical analysis using three different antibodies identified VZV antigen in the cytoplasm of all 11 aortas with pathologically confirmed granulomatous arteritis. Antigen was present in all arterial layers. VZV antigen also was identified in one case of nongranulomatous arteritis and in five of 18 control aortas. Ten of the aortas with granulomatous arteritis contained amplifiable DNA and, of those, seven (70%) contained VZV DNA

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detected by PCR. A records review of the 11 patients who underwent surgical repair of an aortic aneurysm suggested a diagnosis of giant cell arteritis in five cases, whereas none had evidence of Takayasu arteritis.

■ COMMENTARY

This study expands on an earlier study by this same group, which demonstrated VZV in most temporal arteries of patients with GCA, but in only 18% of normal extracranial temporal arteries.[1] Since no inflammation was present in the normal aortas that contained VZV antigen, it is likely that this represented asymptomatic reactivation. It is also unlikely that the VZV in the aortas with either granulomatous arteritis or temporal arteries with GCA represents a nonspecific "bystander" result of tissue inflammation, since VZV is not detected in tissue sections or CSF from patients with a variety of other inflammatory/infectious diseases.[2] In addition, the identification of VZV in all of the arterial layers of the aorta (intima, media, and adventitia) in this study is consistent with findings seen in patients with VZV vasculopathy[3] and GCA.[2]

While strict demonstration of VZV causation in these cases of granulomatous arteritis and GCA has not been proven, it certainly provides a plausible biological linkage. The common temporal association of stroke with recent herpes zoster also has been recognized recently.[4] The potential protective effect of zoster vaccination on prevention of vasculopathy and stroke in adults has yet to be determined, yet seems worthy of study, as well as that of potential antiviral intervention. ■

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ABSTRACT & COMMENTARY

Guideline Update: Adults with Hospital-acquired and Ventilator-associated Pneumonia

By Stan Deresinski, MD, FACP, FIDSA

Clinical Professor of Medicine, Stanford University

Dr. Deresinski reports no financial relationships relevant to this field of study.

SYNOPSIS: The most notable new recommendation of the updated hospital-acquired pneumonia/ventilator-associated pneumonia guideline may be its endorsement of limiting the duration of antibiotic therapy to seven days in most cases.

SOURCE: Kalil AC, Metersky ML, Klompas M, et al. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. *Clin Infect Dis* 2016 Jul 14. [Epub ahead of print].

The Infectious Diseases Society of America, together with the American Thoracic Society, have updated their guideline dealing with the management of adults with hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP). The previous guideline also included the management of healthcare-associated pneumonia (HCAP), a concept that was discarded in the development of this guideline because of evidence that the criteria used for the

designation of HCAP failed to identify infections with antibiotic-resistant pathogens and led to overuse of broad-spectrum antibiotics.

The following is a brief outline of the guideline recommendations. In the guideline, HAP and VAP are discussed together, while in the outline the two are separated for improved clarity.

HOSPITAL-ACQUIRED PNEUMONIA (HAP)

Definitions

Pneumonia is defined as a new lung infiltrate plus clinical evidence that the infiltrate is of an infectious origin, including the new onset of fever, purulent sputum, leukocytosis, and decline in oxygenation. HAP is defined as a pneumonia that arises more than 48 hours after admission.

Diagnosis

Treatment should be based on the results of microbiologic studies performed on respiratory samples obtained noninvasively, rather than being treated only empirically.

Biomarkers and CPIS in Suspected HAP

The diagnosis of HAP should be made based on clinical criteria alone rather than using procalcitonin, CRP, BAL sTREM-1, or CPIS plus clinical criteria in the decision of whether or not to start antibiotic administration.

Initial (Empiric) Antibiotic Treatment

Empiric treatment regimens should be informed by the local distribution of pathogens associated with HAP and their antimicrobial susceptibilities. Include coverage for *Staphylococcus aureus* (not necessarily methicillin-resistant *S. aureus* [MRSA]), *P. aeruginosa*, and other Gram-negative rods (GNR) in all empiric regimens.

Include an antibiotic active against MRSA only in patients with either a risk factor for MRSA infection (prior intravenous antibiotic use within 90 days, hospitalization in a unit where > 20% of *S. aureus* isolates are methicillin resistant or in which the prevalence of MRSA is not known), or who are at high risk for mortality (need for ventilatory support due to HAP, septic shock, or markedly elevated procalcitonin without other reasons [e.g., major surgery]).

If empiric coverage for MRSA is indicated, either vancomycin or linezolid is recommended. For patients without risk factors for MRSA infection and not at high risk of mortality (see above), piperacillin-tazobactam, cefepime, levofloxacin, imipenem, or meropenem provides effective empiric coverage for methicillin-susceptible *S. aureus* (MSSA) infection. (For proven MSSA infection, cefazolin, nafcillin, or oxacillin is recommended.)

For empiric coverage in patients with an increased likelihood of infection with *P. aeruginosa* or other GNRs (IV antibiotic in previous 90 days or a higher risk of mortality [see above]), or cystic fibrosis or structural lung disease (such as bronchiectasis), administer two anti-pseudomonal antibiotics of different classes. Administer one anti-pseudomonal antibiotic to patients for whom these risk factors are absent.

Avoid use of an aminoglycoside as the sole anti-pseudomonal agent.

Pharmacokinetics/Pharmacodynamics

Optimize antibiotic dosing and administration based on PK/PD data.

Definitive Therapy

P. aeruginosa. For patients with HAP due to *P. aeruginosa* who are not in septic shock or at a high risk for death, and for whom the results of antibiotic susceptibility testing are known, monotherapy using an antibiotic to which the isolate is susceptible rather than combination therapy is recommended.

For patients with HAP due to *P. aeruginosa* who are in septic shock or at a high risk for death, and for whom the results of antibiotic susceptibility testing are known, combination therapy using two antibiotics to which the isolate is susceptible rather than monotherapy is suggested. For patients with HAP due to *P. aeruginosa*, the guideline recommends *AGAINST* aminoglycoside monotherapy.

ESBL-Producers. For patients with HAP due to extended spectrum beta-lactamase (ESBL)-producing Gram-negative bacilli, the recommendation is that the choice of an antibiotic for definitive (not empiric) therapy be based upon the results of antimicrobial susceptibility testing and patient-specific factors (e.g., allergies and comorbidities that may confer an increased risk of adverse effects).

Acinetobacter. For patients with HAP caused by *Acinetobacter* species:
If susceptible, treatment with either a carbapenem or ampicillin/sulbactam is suggested.

If susceptible only to colistin, intravenous treatment with a polymyxin (colistin or polymyxin B) is recommended and adjunctive inhaled colistin is suggested; rifampin is not recommended. Tigecycline should not be used.

Carbapenem Resistance. In patients with HAP caused by a carbapenem-resistant GNR susceptible only to polymyxins, an intravenous polymyxin (colistin or polymyxin B) is recommended and adjunctive inhaled colistin is recommended.

Duration, De-escalation of Antibiotic Therapy

The recommended duration of treatment is seven days. De-escalation (e.g., narrowing the coverage spectrum) of empiric therapy, when appropriate, is recommended.

Serum procalcitonin together with clinical criteria, but not CPIS, is suggested to guide discontinuation of antibiotic therapy.

VENTILATOR-ASSOCIATED PNEUMONIA (VAP)

Definitions

Pneumonia is defined as a new lung infiltrate plus clinical evidence that the infiltrate is of an infectious origin, including the new onset of fever, purulent sputum, leukocytosis, and decline in oxygenation. VAP is defined as a pneumonia that arises more than 48 hours after endotracheal intubation.

Diagnosis

Noninvasive sampling (endotracheal aspirate) with semiquantitative culture is recommended. If, however, invasive quantitative cultures are performed, antibiotics should be withheld if diagnostic criteria (PSB: $< 10^3$ CFU/mL; BAL: $< 10^4$ CFU/mL; ETA: $< 10^5$ CFU/mL) are not met.

Biomarkers and CPIS in Suspected VAP. The diagnosis of VAP should be made based on clinical criteria alone rather than by use of either procalcitonin, CRP, BAL sTREM-1, or CPIS plus clinical criteria in the decision of whether or not to start antibiotic administration.

Initial (Empiric) Antibiotic Treatment

Empiric treatment regimens should be informed by the local distribution of pathogens associated with VAP and their antimicrobial susceptibilities. Include coverage for *S. aureus* (not necessarily MRSA), *P. aeruginosa*, and other GNR in all empiric regimens.

Include an antibiotic active against MRSA only in patients with more than one of the following: a risk factor for antimicrobial resistance (IV antibiotic in previous 90 days, septic shock, ARDS preceding VAP, acute renal replacement therapy prior to VAP onset), patients being treated in units where > 10-20% of *S. aureus* isolates are methicillin resistant, and patients in units where the prevalence of MRSA is not known.

If empiric coverage for MRSA is indicated, either vancomycin or linezolid is recommended. To include MSSA in empiric coverage, piperacillin-tazobactam, cefepime, levofloxacin, imipenem, or meropenem is recommended (for proven MSSA infection, cefazolin, nafcillin, or oxacillin is recommended).

For Empiric Coverage of *P. aeruginosa*. Administer two anti-pseudomonal antibiotics of different classes only in patients with more than one of the following: IV antibiotic in previous 90 days, patients in units in which > 10% of GNR isolates are resistant to an agent being considered for monotherapy, and patients in an ICU for which local antimicrobial susceptibility rates are not available.

Administer one anti-pseudomonal antibiotic to patients for whom these risk factors are absent.

Avoidance of aminoglycosides and colistin (or polymyxin B) is recommended if alternative agents with adequate anti-GNR activity are available.

Pharmacokinetics/Pharmacodynamics

Optimize antibiotic dosing and administration based on PK/PD data.

Definitive Therapy

For patients with VAP due to GNR that are susceptible only to aminoglycosides or polymyxins (colistin or polymyxin B), administration of both inhaled and systemic antibiotics, rather than systemic antibiotics alone, is recommended.

***P. aeruginosa*.** For patients with VAP due to *P. aeruginosa* who are not in septic shock or at a high risk for death, and for whom the results of antibiotic susceptibility testing are known, monotherapy using an antibiotic to which the isolate is susceptible rather than combination therapy is recommended.

For patients with VAP due to *P. aeruginosa* who are in septic shock or at a high risk for death, and for whom the results of antibiotic susceptibility testing are known, combination therapy using two antibiotics to which the isolate is susceptible rather than monotherapy is suggested.

For patients with VAP due to *P. aeruginosa*, the recommendation is *AGAINST* aminoglycoside monotherapy.

ESBL-Producers. For patients with VAP due to ESBL-producing Gram-negative bacilli, it is recommended that the choice of an antibiotic for definitive (not empiric) therapy be based upon the results of antimicrobial susceptibility testing and patient-

specific factors (e.g., allergies and comorbidities that may confer an increased risk of adverse effects).

Acinetobacter. For patients with VAP caused by *Acinetobacter* species:
If susceptible, treatment with either a carbapenem or ampicillin/sulbactam is suggested.

If susceptible only to colistin, intravenous treatment with a polymyxin (colistin or polymyxin B) is recommended and adjunctive inhaled colistin is suggested; rifampin is not recommended. Tigecycline should not be used.

Carbapenem Resistance. In patients with VAP caused by a carbapenem-resistant GNR susceptible only to polymyxins, an intravenous polymyxin (colistin or polymyxin B) is recommended and adjunctive inhaled colistin is recommended.

Duration, De-escalation of Antibiotic Therapy
The recommended duration of treatment is seven days. De-escalation (e.g., narrowing the coverage spectrum) of empiric therapy, when appropriate, is recommended.

Serum procalcitonin together with clinical criteria, but not CPIS, is suggested to guide discontinuation of antibiotic therapy.

Ventilator-Associated Tracheitis (VAT)
In patients with VAT, antibiotic therapy is not recommended. ■

ABSTRACT & COMMENTARY

Antibiotics, Breastfeeding, and the Intestinal Microbiota

By Philip R. Fischer, MD, DTM&H

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Dr. Fischer reports no financial relationships relevant to this field of study.

SYNOPSIS: Breastfeeding is associated with less frequent bacterial infections and with less subsequent obesity. Using antibiotics reduces or removes these favorable effects of breastfeeding, perhaps via alterations in the intestinal microbiota.

SOURCE: Korpela K, Salonen A, Virta LJ, et al. Association of early-life antibiotic use and protective effects of breastfeeding: Role of the intestinal microbiota. *JAMA Pediatr* 2016;170:750-757.

The exact mechanisms by which breastfeeding reduces the frequency of infection and the risk of obesity are unknown. However, it is known that breastfeeding affects patterns of intestinal bacterial flora, and that microbiome patterns relate to risks of infection and obesity. Finnish investigators explored the links between early antibiotic use, breastfeeding, and intestinal microbiota.

The study cohort included 226 children, 142 of whom provided stool samples for microbiota analysis. Study subjects were generally healthy, attended day care, and resided in the same region of northern Finland.

The mean duration of breastfeeding was eight (range 0-18) months. By ages 1 and 2 years, respectively, 57% and 88% of children had received at least one course of antibiotic treatment. Half of children received antibiotics before weaning; the other half did not.

Breastfeeding was associated with a marked reduction in bacterial infections (as seen by the proxy of antibiotic use). Each month of breastfeeding related to a 6% reduction of antibiotic use during the first year of life. However, using antibiotics once reduced the effect of breastfeeding on subsequently reduced infections to just 4% per month. A favorable effect of breastfeeding on subsequent antibiotic use persisted, even after weaning.

Similarly, each month of breastfeeding was associated with a 0.08 unit reduction in BMI z score. However, this reduction was not seen in breastfed babies who received antibiotics.

Differences in microbiota composition in the 42 children who underwent full analysis were mainly driven by early antibiotic use and the duration of breastfeeding. Short duration breastfeeding and early antibiotic use similarly altered stool flora toward fewer bifidobacteria and more *Clostridia*.

Early antibiotic use partially negated the otherwise favorable effects of breastfeeding on intestinal microbiota and, thus, on subsequent infections and obesity.

■ COMMENTARY

In 2014, *Infectious Disease Alert* reviewed evidence that use of antibiotics during infancy increases the risk of childhood obesity.[1] These new data reinforce this idea and provide further understanding of a potential mechanism for the interaction. As elaborated in an editorial accompanying the Finnish paper, the intestinal microbiota composition regulates host metabolic status by producing short-chain fatty acids that then influence the secretion of various peptides that regulate motility, absorption, and satiety. Altering the intestinal microbiota can disrupt small bowel integrity and function in ways that translocate lipopolysaccharides (endotoxins) and trigger low-grade inflammation as is seen in chronic obesity.[2]

Bifidobacteria are present in human milk, and the predominance of these organisms in infant intestinal microbiota is associated with breastfeeding.[3] These bacteria are less common in microbiota of pre-term babies and in babies delivered by cesarean section, perhaps explaining some of the increase in infection in these populations.[3]

Antibiotic use, either by the laboring mother[3] or the baby, is associated with alterations in intestinal flora. These alterations, downgrading bifidobacteria and upgrading clostridial species, are associated with increases in subsequent bacterial infections. Clearly, antibiotics (especially broad-spectrum antibiotics) should be used judiciously.[2] Further research is needed to see if the use of probiotics or supplementation of omega-3 fatty acids (as found in breastmilk) can maintain or restore the virginal intestinal microbiota.[2]

There are several factors that influence intestinal flora and the subsequent risk of infection (and even allergy and obesity).[4] It has been suggested that rather than focusing on over-cleaning based on the "hygiene hypothesis," we should advocate a combination of strategies to help restore the microbiome: natural childbirth, breastfeeding, social exposure through outdoor activities, diet, and appropriate antibiotic use.[4] For those of us dealing with potentially infected children, these new data and discussions serve as yet another call to be judicious about our use of antibiotics in infants. ■

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ABSTRACT & COMMENTARY

Steroids Increase the Risk for Community-acquired *Staphylococcus aureus* Bacteremia

By Richard R. Watkins, MD, MS, FACP

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Dr. Watkins reports that he has received research support from Actavis.

SYNOPSIS: A case-control study observed an increased risk for developing community-acquired *Staphylococcus aureus* bacteremia with the use of systemic glucocorticoids. A distinct dose-response relationship was found.

SOURCE: Smit J, Kaasch AJ, Sogaard M, et al. Use of glucocorticoids and risk of community-acquired *Staphylococcus aureus* bacteremia: A population-based case-control study. *Mayo Clin Proc* 2016;91:873-880.

Staphylococcus aureus bacteremia (SAB) continues to cause significant morbidity and mortality. Previous studies produced conflicting results about whether steroids increase the risk of SAB and may have been biased by confounding variables. Therefore, Smit and colleagues sought to more clearly define the risk of SAB associated with the use of steroids.

The investigators used data collected from a population-based registry from northern Denmark. They chose to limit the study to patients with community-acquired SAB (CA-SAB), defined as no previous diagnosis of SAB within five years, because patients with previous SAB are at increased risk for recurrences compared to the general population. Current steroid users were defined as patients whose most recent prescription redemption was within 90 days before the index date. This group was further characterized into new users, defined as those who redeemed their first-ever prescription within 90 days of the index date, and long-term users who redeemed their prescription within 180 days. Former users were defined as those patients whose last prescription was 90 to 180 days before the index date, and nonusers were persons who filled no prescriptions for steroids within 180 days of the index date. Prescriptions for inhaled and topical steroids were excluded. Risk for CA-SAB was further assessed among current steroid users according to prednisolone-equivalent cumulative doses, from 150 mg or less up to greater than 1,000 mg. Conditional logistic regression was used to calculate crude and adjusted odds ratios (ORs).

A total of 2,638 patients with CA-SAB were identified, of whom 379 were current users of steroids, along with 26,379 randomly selected controls (1:10 ratio), which included 827 current steroid users. Only 5% of the isolates were methicillin-resistant *Staphylococcus aureus* (MRSA). Compared to controls, patients with CA-SAB had more co-morbidities, including diabetes (18% vs. 5%), chronic pulmonary diseases (14% vs. 6%), and cancer (25% vs. 7%). The adjusted OR for CA-SAB among new steroid users was 2.73 (95% CI, 2.17-3.45), 2.31 (95% CI, 1.90-2.82) for long-term users, and 1.33 (95% CI, 0.98-1.81) for former users. Also, the risk of CA-SAB increased with escalating doses of steroids. Compared to nonusers, the adjusted OR ranged from 1.32 (95% CI, 1.01-1.72) for those taking a cumulative dose ≤ 150 mg, up to 6.25 (95% CI, 4.74-8.23) for those with a cumulative dose > 1,000 mg. Finally, there were no significant differences in the risk of CA-SAB based on sex or age.

■ COMMENTARY

The results of this study showed there was a considerable risk of developing CA-SAB for patients in the cohort who were taking steroids. Furthermore, the risk increased with higher steroid doses. Smit and colleagues were astute for excluding cases of hospital-acquired SAB, which likely would have introduced confounding variables, such as post-surgical wound infections and SAB caused by intravenous catheters. Although the prevalence of MRSA bacteremia was very low compared to that of the United States, there is no logical reason to suspect that a higher rate of MRSA would have led to any different outcomes.

[The results of this study showed there was a considerable risk of developing CA-SAB for patients in the cohort who were taking steroids.]

As the authors mention, there are several pathophysiologic mechanisms by which steroid use might predispose to CA-SAB. For example, steroids inhibit toll-like receptor signaling, a key component in the innate immune response to *S. aureus* infections. Furthermore, steroids reduce phagocytosis, cytokine production, and leukocyte adhesion. Previous studies have demonstrated that the adverse effects of steroids on immunity are dependent on the length of therapy and the dosage used. Wound healing also is impaired by steroids, and this loss of skin barrier protection can allow *S. aureus* to enter deeper tissues and, ultimately, the bloodstream.

Despite the interesting findings of the study, a few words of caution are necessary. First, there were no data on steroid adherence among the patients or on infective foci, such as vascular access devices. Second, patients who use steroids tend to be sicker than the general patient population and, thus, more likely to be susceptible to CA-SAB. Third, the study was conducted in northern Denmark, and the results might not be generalizable to other populations and geographic areas.

What is the take-home message from this study? Clinicians should maintain a high level of suspicion for CA-SAB in patients taking steroids and focus accordingly, i.e., blood cultures and a thorough history and physical examination, with particular attention to joint or back pain and new heart murmurs that might indicate an infected joint, discitis, or endocarditis. ■

ABSTRACT & COMMENTARY

Rotavirus Vaccination Prevents Febrile Seizures in Children

By Dean L. Winslow, MD, FACP, FIDSA

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Dr. Winslow reports no financial relationships relevant to this field of study.

SYNOPSIS: In Queensland, Australia, rotavirus vaccine was shown to be 36% effective in preventing emergency department (ED) presentation for febrile seizures among children up to two years following vaccination.

SOURCE: Sheridan SL, Ware RS, Grimwood K, Lambert SB. Febrile seizures in the era of rotavirus vaccine. *J Ped Infect Dis Soc* 2016;5:206-209.

Vaccine effectiveness in preventing ED presentation and subsequent hospitalization for febrile seizures was calculated using routinely collected health data. The method used involved comparing the proportion of children with febrile seizures who were vaccinated with rotavirus vaccine (PCV) with the proportion of the target population vaccinated (PPV). PPV values were obtained from the Australian Childhood Immunisation Registry (ACIR). To determine PCV, Queensland Health Data Linkage unit used data-matching software to probabilistically match vaccination data with ED presentation data. vaccine efficacy (VE) was assessed over an observation period of one year for 12-month birth cohorts.

During the study period, there were 2,211 ED presentations for febrile seizures, and 635 (29%) children were hospitalized. Among children between 8 months of age and 31 months of age, VE for the full three-dose rotavirus vaccine series in preventing febrile seizures resulting in ED visit was 36%, and 38% for prevention of subsequent hospitalization. This protective effect of rotavirus vaccination persisted up to four years after vaccination.

■ COMMENTARY

The VE of 36% for prevention of any febrile seizure is generally consistent with the U.S. finding of a 21% reduction of all childhood seizures requiring ED care or hospitalization in the first year after rotavirus vaccination.[1] The use of the Queensland linked dataset demonstrated a more profound effect, likely because of its ability to tease out febrile from afebrile seizures. Since serologic studies and/or viral isolation or polymerase chain reaction (PCR) was not performed in this study, the precise mechanism of the rotavirus vaccination's protective effect on febrile seizures in these young children is not completely established.

Interestingly, another U.S. study showed that rotavirus infection was associated with new onset of febrile seizures in 8% of children and in 21% of children presenting with afebrile seizures.[2]

[... the precise mechanism of the rotavirus vaccination's protective effect on febrile seizures in these young children is not completely established.]

One potential source of confounding in this Queensland study was that it may have been more likely that children who received rotavirus vaccine also were more likely to have received influenza B vaccine (another common cause of febrile seizures). In any case, the results are very positive and demonstrate an additional unanticipated beneficial protective effect of rotavirus vaccination on preventing childhood seizures, in addition to its efficacy in preventing the most common cause of childhood diarrhea seen in the developed world. ■

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PHARMCOLOGY UPDATE

Sofosbuvir and Velpatasvir Tablets (Epclusa)

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

Dr. Elliott is Medical Director, Pharmacy, Northern California Kaiser Permanente, and Assistant Clinical Professor of Medicine, University of California, San Francisco. Dr. Chan is Pharmacy Quality and Outcomes Manager, Kaiser Permanente, Oakland, CA.

Drs. Elliott and Chan report no financial relationships relevant to this field of study.

The FDA has approved the first drug combination for the treatment of all six major genotypes of hepatitis C virus (HCV) infections. The combination contains a previously approved nucleotide analog NS5B polymerase inhibitor, sofosbuvir (SOF), and a newly approved HCV NS5A inhibitor velpatasvir (VEL). SOF/VEL is marketed as Epclusa.

INDICATIONS

SOF/VEL is indicated for the treatment of adult patients with chronic HCV genotype 1, 2, 3, 4, 5, or 6 infections.[1] It is approved for patients without cirrhosis, with compensated cirrhosis, or with decompensated cirrhosis (in combination with ribavirin).

DOSAGE

For patients without cirrhosis or with compensated cirrhosis, the recommended dose is one tablet once daily for 12 weeks.[1] For patients with decompensated cirrhosis, the recommended dose is one tablet with weight-based ribavirin for 12 weeks. No dose adjustments are needed for mild-to-moderate renal impairment or mild, moderate, or severe hepatic impairment. Each tablet of SOF/VEL contains 400 mg of sofosbuvir and 100 mg of velpatasvir.

POTENTIAL ADVANTAGES

This is the first drug/drug combination approved for the treatment of the six most prevalent HCV genotypes, as well as for patients with or without cirrhosis.

POTENTIAL DISADVANTAGES

Coadministration of sofosbuvir and amiodarone is not recommended because of potential risk of serious symptomatic bradycardia.[1] Concomitant use with P-gp inducers or moderate to potent inducers of CYP2B6, CYP2C8, or CYP3A4 also is not recommended. Take precautions with concomitant administration with antacids or histamine-2 receptor antagonists. Avoid proton pump inhibitors unless medically necessary.[1]

COMMENTS

The safety and efficacy of SOF/VEL were evaluated in three trials in patients without cirrhosis or with compensated cirrhosis.[1,2,3] A fourth included subjects presenting with decompensated cirrhosis.[1,4] The primary endpoint was no detectable virus at 12 weeks post-treatment (SVR12).

In the first study, subjects with genotype 1, 2, 4, 5, and 6 were randomized to SOF/VEL for 12 weeks (n = 624) or placebo (n = 116).[1,2] SVR12 ranged from 97% to 100%, compared to 0% for placebo.

Study two compared SOF/VEL for 12 weeks (n = 134) to SOF + ribavirin for 12 weeks (n = 132) in subjects with genotype 2.[1,3] SVR12 rates were 99% vs. 94%. Relapse rates were 0% vs. 5%, respectively.

[The safety and efficacy of SOF/VEL were evaluated in three trials in patients without cirrhosis or with compensated cirrhosis.]

Study three compared SOF/VEL for 12 weeks (n = 277) and SOF + ribavirin for 24 weeks (n = 275) in subjects with genotype 3.[1,3] Overall, SVR12 rates were 95% compared to 80% (treatment difference of 14.8%; 95% confidence interval, 9.6-20%). SOF/VEL was more effective in treatment-naïve and treatment-experienced without cirrhosis (98% vs. 90%; 94% vs. 71%, respectively). In those with compensated cirrhosis, SVR12 rates were 93% vs. 73%, and 89% vs. 58%, respectively.

Study four compared three regimens: SOF/VEL for 12 weeks, SOF/VEL + ribavirin for 12 weeks, or SOF/VEL for 24 weeks in subjects with genotype

1, 2, 3, 4, and 6 with decompensated cirrhosis.[1,4] Overall, SVR12 rates were 83%, 94%, and 86%, respectively. The most frequently reported adverse events for monotherapy included headache (22%) and fatigue (15%).[1] In combination with ribavirin, adverse events included fatigue (32%), anemia (26%), nausea (15%), headache (11%), insomnia (11%), and diarrhea (10%).

CLINICAL IMPLICATIONS

SOF/VEL has been highly anticipated, as it is the first combination that provides an effective treatment for all genotypes as well as patients presenting with moderate-to-severe cirrhosis. The cost of SOF/VEL (without ribavirin) is $74,760 for 12 weeks of therapy. ■

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Infectious Disease [ALERT]

Updates

By Carol A. Kemper, MD, FACP

Travel Recommendations for Hajj

SOURCE: *Weekly Epidemiological Record* no. 26/27; July 1, 2016:331-340.

Travel to the Middle East for Hajj has regained its popularity, with an estimated 2 million people anticipating travel to Mecca this September. Many will stay in the massive tent city, Mina, 8 km outside of the city, where conditions are crowded. Recommendations for travel for Hajj, based on the World Health Organization (WHO) guidelines, were last published in *Infectious Disease Alert* in 2012. The following is a summary of current recommendations for travel to Hajj published in the *Weekly Epidemiological Record* last month, as well as other appropriate suggestions. In addition to the following requirements and recommendations for entry visas to Hajj and Umrah 2016, the Saudi government plans to provide electronic bracelets for visitors to improve security.

• **Meningococcal Vaccine:** Proof of meningococcal vaccination with the tetravalent vaccine ACYW135 is required for all travelers 2 years of age or older to obtain a visa. Both polysaccharide and conjugate vaccines are acceptable, but the name of the vaccine must be clearly spelled out on the vaccine card. The vaccine must be administered not less than 10 days nor more than three years before arrival. In addition, to reduce the carrier rate, the Saudi Arabian Ministry of Health will administer prophylactic antibacterials (ciprofloxacin 500 mg x 1) to adults and children older than 12 years of age arriving from the African continent.

• **Polio:** For those traveling from the United States and regardless of a prior history of polio vaccination, you must show proof of receipt of at least one dose of oral polio vaccine (OPV) or inactivated poliovirus vaccine (IPV) within the previous 12 months and not less than four weeks prior to departure. In addition, travelers from countries endemic for polio will receive one dose of OPV at border points on arrival to Saudi Arabia.

• **Influenza:** Annual influenza vaccination is recommended, especially for pregnant women, the elderly, those with chronic health conditions, and small children.

• **MMR and Tdap:** Current vaccination is routinely recommended.

•**Hepatitis B Vaccine (HBV):** A common ritual for men participating in Hajj is to have their heads shaved. While licensed barbers legally are required to employ a fresh blade with each new customer, illegal street vendors may not follow the law. It is therefore recommended that travelers consider HBV vaccination.

• **Malaria:** Malaria is not present in Mecca, although it is present in the southwestern areas of Saudi Arabia. Travelers planning to visit this more rural region should consider malaria prophylaxis.

• **Yellow Fever:** Certification of vaccination is required only if

arriving from a country or area at risk for yellow fever.

• **Dengue and Zika Viruses:** The mosquito that carries dengue virus, *Aedes aegypti*, has not been detected in Hajj or Umrah area for many years, although it may be found elsewhere in Saudi Arabia, and theoretically carries a risk of dengue and other viral agents. Zika virus has not been detected in Saudi Arabia.

• **Specific Recommendations for Women:** Women should consider hormonal therapy to avoid having a menstrual cycle at this time.

• **General Recommendations:** Practice good hand washing; wear regular surgical masks in crowded places or when in contact with ill persons; do not drink raw camel milk or camel urine or eat inadequately cooked meat; drink plenty of fluids and replenish electrolytes in the heat.

Dung and Tetracycline

SOURCE: Hammer TJ, Fierer N, Hardwick B, et al. Treating cattle with antibiotics affects greenhouse gas emissions, and microbiota in dung and dung beetles. *Proc Biol Sci* 2016;283.

In one of the first studies of its kind, these authors examined the effect of antibiotic administration to cattle on dung beetle microbiota and gas emissions from cow patties in the field. Antibiotics have significant effects on livestock gut microbiota, which could affect the gut flora of dung beetles, and may have cascading environmental effects.

Fresh samples of dung were collected from five cows treated for three days with tetracycline and from five untreated control cows. The dung then was separated into patties and placed in the field. Dung beetles (*Aphodius fossor*) were added to two-thirds of the patties, and then samples of the dung were analyzed at various intervals for up to 73 days for beetle content, microbial flora, and gas emissions. This duration of time was sufficient to gauge any effect on the next generation of dung beetles and their larvae. Efflux of methane, carbon dioxide, and nitrous oxide was measured.

Beetles' density, weight, and sex were measured at intervals, and microbial flora analyzed using 16s rRNA primers and sequencing. Administration of tetracycline to the target animal had no effect on beetle size, reproductive capacity, or survival. Larval weight was unaffected, and the number of offspring was similar between treated and control cow patties. The use of antibiotics in the target animal had a clear effect on beetle microbiota, however. Generally, beetles have a less diverse microbiota than their diet. While dung was dominated by *Clostridia*, spirochetes, and *Bacteroidia*, less than 1% of dung microbiota was present in the beetles, the latter of which were dominated by bacilli and other proteobacteria/gammaproteobacteria (more of what is referred to as "archaea"). In other words, the beetles completely transform what they're eating, and dominant beetle microbes are rare in dung. Despite this, antibiotic treatment had a clear effect on the dung beetles' microbiota — although it's not clear whether this was a "nutritional effect" or how this occurred.

Generally, the presence of beetles in dung diminishes efflux of methane from cow patties. In contrast, methane gas emissions from dung from treated animals were increased by > 100%. Efflux of CO_2 and N_2O were similar from treated and untreated cows' patties.

The effect of tetracycline on target livestock was nowhere near as great as the mortal effect of certain antiparasiticides (e.g., ivermectin and other avormectins) — which destroy the dung beetles in excrement for months and months — leaving undigested cow and sheep patties to solidify like fossilized rocks in the field. ■

CME INSTRUCTIONS

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

1. Which of the following is associated with an increased risk of subsequent bacterial infection during infancy?

a. Longer breastfeeding duration

b. Antibiotic use during the early months of life

c. More bifidobacteria and fewer *Clostridia* in the infant intestinal microbiota

d. High levels of dietary omega-3 fatty acids

2. Which of the following is correct regarding sofosbuvir/velpatasvir (Epclusa) treatment of chronic HCV infection?

a. It is approved for use for infections with all genotypes except 2 and 3.

b. It is approved for use for infections with all genotypes except 1 and 4.

c. It is approved only for infection due to genotype 1.

d. It is approved for infections due to all genotypes.

3. Which of the following is correct with regard to the 2016 updated guideline on management of hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP)?

a. The recommended duration of antibiotic therapy in most cases is only seven days.

b. Monotherapy with an aminoglycoside is recommended for treatment of infections due to *Pseudomonas aeruginosa*.

c. All patients with HAP should undergo diagnostic bronchoscopy.

d. The decision to initiate empiric antibiotic therapy should be dependent on the procalcitonin level rather than on clinical criteria.

CME OBJECTIVES

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

- discuss the diagnosis 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.