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Infectious Disease [ALERT]

Incisive Commentary and Clinical Abstracts on Current Issues in Infectious Diseases

ABSTRACT & COMMENTARY

Vancomycin Combined with Piperacillin-Tazobactam Increases the Risk for Acute Kidney Injury

By Richard R. Watkins, MD, MS, FACP, FIDSA

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

SYNOPSIS: A retrospective cohort study found an increased risk of acute kidney injury for patients who received vancomycin in combination with piperacillin-tazobactam compared to those who received vancomycin plus cefepime (hazard ratio = 4.27; 95% confidence interval, 2.73-6.68).

SOURCE: Navalkele B, Pogue JM, Karino S, et al. Risk of acute kidney injury in patients on concomitant vancomycin and piperacillin-tazobactam compared to those on vancomycin and cefepime. *Clin Infect Dis* 2017;64:116-123.

The combination of vancomycin and piperacillin-tazobactam is used frequently in clinical practice. This regimen covers many community and nosocomial pathogens and often is chosen empirically for sepsis. However, recent reports have noted an increased risk for acute kidney injury in patients given concurrent vancomycin and piperacillin-tazobactam. Therefore, Navalkele and colleagues sought to clarity this association and determine if there is a similar risk when vancomycin is paired with cefepime.

The study was a retrospective, matched, cohort study from a single healthcare institution. Inclusion criteria included age ≥ 18 years and having received combination therapy with vancomycin and cefepime or vancomycin and piperacillin-tazobactam for at least 48 hours, with the two

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antibiotics administered within 24 hours of each other. Patients were excluded if their baseline creatinine was > 1.2 mg/dL or if they required dialysis. They were divided into two groups based on the combination received and matched using five variables that are associated with the development of acute kidney injury. These included sepsis severity, ICU status at onset of combination therapy, duration of combination therapy, daily dose of vancomycin received, and number of concomitant nephrotoxic agents received while on combination therapy. Also, to assess the effect of vancomycin on acute kidney injury, the researchers calculated the median trough of vancomycin prior to the onset of acute kidney injury.

There were 279 pairs included in the study population totaling 558 patients. The mean age was 55.9 years and the baseline characteristics were similar between the two groups. Patients who received the vancomycin/piperacillin-tazobactam combination had a higher incidence of septic shock and skin and soft tissue infections. The rate of acute kidney injury was higher in those who received vancomycin/piperacillin-tazobactam vs. vancomycin/cefepime (29.0% vs. 11.1%; hazard ratio [HR] = 4.0; 95% confidence interval [CI], 2.6-6.2; $P < 0.001$). After controlling for differences between the two groups, multivariate analysis found vancomycin/piperacillin-tazobactam was independently associated with the development of acute kidney injury (HR = 4.3; 95% CI, 2.7-6.7; $P < 0.001$). Furthermore, the median time to onset of acute kidney injury was shorter in the vancomycin/piperacillin group (three days) compared to the vancomycin/cefepime group (five days; $P < 0.001$).

While there was no difference in mortality between the two groups, those who received vancomycin/piperacillin-tazobactam had a longer median length of stay (eight days) compared to the vancomycin/cefepime group (six days; $P = 0.01$). The two groups had similar median vancomycin trough levels. However, while no association was found between median trough levels and acute kidney injury in the vancomycin/piperacillin-tazobactam group, a direct relationship was seen for those in the vancomycin/cefepime group. Acute kidney injury occurred in 1% of vancomycin/cefepime patients, with mean vancomycin troughs < 15 mg/L, in 5% of those with median troughs between 15 mg/L and 20 mg/L, and in 21% of those with troughs > 20 mg/L.

■ COMMENTARY

The study by Navalkele and colleagues is interesting because it brings to mind the old yet still salient principle of *primum non nocere*. It is notable that the rate of acute kidney injury was three times higher in patients who received vancomycin/piperacillin-tazobactam compared to those who received vancomycin/cefepime. But what is the pathophysiological mechanism that can explain this result?

[... clinicians should be aware of the potential for acute kidney injury and carefully weigh the risks and benefits.]

It does not appear to be directly related to vancomycin toxicity, since there were no differences in the median vancomycin troughs between the two groups. Indeed, both cefepime and piperacillin/tazobactam are β-lactam antibiotics primarily metabolized through the kidneys and similarly require dosage adjustment with impaired renal function. The investigators did not attempt to further characterize the type of acute kidney injury or speculate about their findings. However, β-lactams are known to cause acute interstitial nephritis, and perhaps vancomycin somehow magnifies this risk. Ideally, a prospective, randomized clinical trial should be conducted to clarify the risk of acute kidney injury and elucidate the underlying etiology. Whether such a trial could be funded remains to be seen.

Like previous retrospective studies that also showed an increased risk of acute kidney injury with vancomycin and piperacillin-tazobactam, the study by Navalkele and colleagues may have been influenced by unmeasured confounding

variables, limiting the generalizability of the findings. Despite this, clinicians should be aware of the potential for acute kidney injury and carefully weigh the risks and benefits. Given that the median onset of acute kidney injury was three days, one reasonable approach would be to de-escalate therapy based on culture data, which often are available by 48-72 hours. Indeed, this is a circumstance in which rapid diagnostic testing would be valuable. ■

ABSTRACT & COMMENTARY

Inflammation in HIV Also Is Mediated by CD8+ T-cells and Platelets

By Dean L. Winslow, MD, FACP, FIDSA

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

SYNOPSIS: CX3CR1+ CD8+ T-cells home to vascular endothelium and are enriched in ART-treated patients with HIV. These cells may play an important role in CVD risk in HIV-infected patients.

SOURCE: Mudd JC, Panigrahi S, Kyi B, et al. Inflammatory function of CX3CR1+ CD8+ T cells in treated HIV infection is modulated by platelet interactions. *J Infect Dis* 2016;214:1808-1816.

Researchers studied cells obtained from 35 HIV-infected patients receiving ART and 17 HIV-negative controls. PBMCs were purified by standard Ficoll-Hypaque centrifugation and isolated using a MACS Pro separator. Flow cytometry was used to characterize both lymphocyte and platelet populations and to look at cytokine production and cell surface marker expression. The researchers isolated platelets and specifically examined them for CD62P and TGF-B expression using flow cytometry. Cultures of PBMCs, T-cells, and T-cells with purified platelets were incubated with various concentrations of thrombin. In other experiments, anti-TGF-B was added to the cultures.

The main results included the following: 1) CX3CR1 identified a population of circulating memory T-cells; 2) CX3CR1+ CD8+ T-cells express the thrombin receptor PAR-1; 3) PAR-1 activation influences CD8+ T-cell function; 4) Platelet-derived TGF-B impairs CD8+ T-cell function.

■ COMMENTARY

This paper nicely shows that CX3CR1+PAR-1+ T-cells are increased in antiretroviral-treated HIV patients. Because this population of cells has a known ability to interact with vascular endothelium, thrombin, and platelets, this subset of T-cells likely contributes to thrombosis, accelerated atherosclerosis, and cardiovascular disease (CVD) that is known to complicate HIV infection.

It has been known for some time that HIV induces a "pro-inflammatory" state that, unfortunately, is not completely reversed even in the presence of fully suppressive ART. Past research has placed much emphasis on the early occurrence of CD4+ T-cell depletion from gut-associated lymphoid tissue in the setting of HIV infection, increased neutrophil infiltration, and apoptosis in the small intestine, and increased microbial translocation — which is thought to drive the observed increase in pro-inflammatory cytokines (IL-6, SCD14), acute phase reactants (hs-CRP), and activation of coagulation (D-dimer). This pro-inflammatory state also is linked to increased LDL/Apo-B and reduced HDL/Apo-A1. All of these factors are thought to contribute to the accelerated atherosclerosis and CVD that is seen in HIV.

[This study demonstrates the likely contribution of CD8+ T-cells, platelets, and their interaction with the coagulation system in this complicated process.]

This study demonstrates the likely contribution of CD8+ T-cells, platelets, and their interaction with the coagulation system in this complicated process. Perhaps in the future we will have targeted therapies to address these factors. ■

ABSTRACT & COMMENTARY

Does Tonsillectomy Decrease Throat Infections?

By Philip R. Fischer, MD, DTM&H

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

SYNOPSIS: For children with recurrent throat infections, tonsillectomy leads to fewer throat infections and less school absence during the first post-operative year (as compared to similar children who did not undergo tonsillectomy). However, beneficial effects of surgery do not persist over time.

SOURCE: Morad A, Sathe NA, Francis DO, et al. Tonsillectomy versus watchful waiting for recurrent throat infection: A systematic review. *Pediatrics* 2017;139:e20163490.

Tonsillectomy often is performed for recurrent throat infections. Research studies of beneficial outcomes of tonsillectomy, however, have used varied definitions of "recurrent infections," measures of outcomes, and durations of follow-up. Morad and colleagues, therefore, undertook a rigorous systematic review of the literature to determine the actual benefits of tonsillectomy for recurrent infection.

A comprehensive review of the English-language literature centered on tonsillectomy and throat infections. Comparative studies were included, whether the investigations were randomized, controlled trials or either prospective or retrospective cohort studies. The initial broad search identified 9,608 article citations. Seven studies met inclusion criteria and were assessed to have only low or moderate risk of bias. Of these seven studies that were included in the analysis, four were randomized, controlled trials, one was a non-randomized trial, and two were retrospective cohort studies. These seven studies were published during the years 2002 to 2015.

The reviewed studies revealed important findings. Children undergoing tonsillectomy had fewer recorded days of sore throat during the year after the procedure than did children managed medically (1.0 episode per month prior to the intervention or starting time, 0.50 vs. 0.64 sore throat episodes during the first follow-up year). After tonsillectomy, children had 1.74 medical visits for sore throat during the first post-operative year as compared to 2.93 in similar patients not treated surgically. Children who did not have their tonsils removed were 3.1 times more likely to test positive for group A streptococci than those treated with tonsillectomy. There was less missed school during the first year of follow-up if patients were treated with tonsillectomy; there was no statistically significant difference in school absence between groups during the second and third years of follow-up. There were not enough large studies with good follow-up over multiple years to identify any lasting benefit of tonsillectomy in reducing infections after the first post-operative year.

Three studies reported quality-of-life data. There were no differences in measured quality of life between the surgical and non-surgical treatment groups.

The researchers concluded that "tonsillectomy can produce short-term reduction in throat infections compared with no surgery in children" with recurrent throat infections during the preceding one to three years and that there were also fewer missed school days and fewer medical visits needed in the children treated surgically. However, these beneficial effects did not persist after the first post-treatment year.

■ COMMENTARY

Why do some of us climb mountains? Because they are there. And, why do some surgeons remove tonsils? As the semi-tongue-in-cheek joke responds, because they are there.

Tonsillectomy, with or without adenoidectomy, is one of the most common surgical procedures in the United States. The current tonsillectomy "rate" is approximately two per 1,000 children.[1]

In fact, recurrent throat infection is accepted as an appropriate indication for tonsillectomy in children. Morad and colleagues have contributed to our understanding and clinical care by rigorously reviewing decades of outcomes literature and,

in the process, quantifying the actual benefits of tonsillectomy.

Indeed, for children with at least three throat infections per year prior to surgery, tonsillectomy was associated with reduced infection and reduced school absence during the first post-tonsillectomy year. All children, as they aged, had some reduction in infection and absence, but the reductions were more marked in the children treated surgically.

This new systematic review did not look at complications of tonsillectomy. Of course, any benefit even extending through the first post-operative year must be balanced against potential complications. Tonsillectomy does carry cost, a slight risk of serious complications, and relatively frequent (about 20%) risks for significant discomfort, poor oral intake, and bleeding.[1] Sub-total intracapsular tonsillectomy has lower complication rates, but it is not yet known whether application of this previously used new-again approach is equally effective in reducing throat infections.[1]

Recurrent infection is not, however, the only indication for tonsillectomy. In fact, more tonsillectomies now are performed for obstructive rather than infectious indications.[2] Some of Morad's colleagues concurrently reported a systematic review of benefits of tonsillectomy for sleep-disordered breathing and found good short-term improvement in sleep outcomes compared with no surgery in children with obstructive sleep-disordered breathing.[3] Again, evidence of longer-term favorable outcomes was lacking.[3]

Tonsillectomy often is combined with adenoidectomy, especially in young children. The combined surgical procedures can help improve drainage of ear fluid and decrease risks for hearing loss in patients with persistent otitis media with effusion.[4]

What do parents think? Some parents have doubts about the value of subjecting a child to tonsillectomy. A recent report found that parents with doubts entering the operation are more likely to regret having the operation afterward.[5] This is a reminder that physicians and parents considering tonsillectomy for a child should be fully informed and confident pre-operatively to avoid whatever regrets might follow later. ■

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ABSTRACT & COMMENTARY

Antibiotic Treatment in Community-acquired Pneumonia

By Kathryn Radigan, MD

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

SYNOPSIS: In patients with newly diagnosed community-acquired pneumonia, basing the duration of antibiotic treatment on clinical stability criteria led to a significant reduction in duration of antibiotic treatment without an increased risk of adverse outcomes.

SOURCE: Uranga A, España PP, Bilbao A, et al. Duration of antibiotic treatment in community-acquired pneumonia: A multicenter randomized clinical trial. *JAMA Intern Med* 2016;176:1257-1265.

Although the Infectious Diseases Society of America (IDSA)/American Thoracic Society (ATS) guidelines suggest a minimum of five days of treatment in patients with one or more community-acquired pneumonia (CAP)-associated instability criteria and who achieve an afebrile state for 48-72 hours, the optimal length of antibiotic treatment has not been formally investigated. To determine whether the duration of antibiotic treatment based on IDSA/ATS criteria was as effective as conventional

treatment, Uranga et al conducted a multicenter, noninferiority, randomized, clinical trial performed at four teaching hospitals in Spain. From Jan. 1, 2012, through Aug. 31, 2013, 312 hospitalized patients diagnosed with CAP were randomized to an intervention or control group on day five of their hospitalization.

Pneumonia was defined as a new pulmonary infiltrate on chest X-ray in addition to at least one symptom compatible with pneumonia, including cough, fever, dyspnea, and/or chest pain. Patients were excluded if they were infected by HIV, exhibited chronic immunosuppression, resided in a nursing home or previously were in an acute care hospital/palliative care unit, ingested antibiotics within the previous 30 days, required a longer course of antibiotics based on identification of bacteria, required a chest tube, or presented with extrapulmonary infection. For patients randomized to the intervention group, treatment with antibiotics continued for a minimum of five days, with cessation of treatment at that time if their body temperature was ≤ 37.8°C for 48 hours and they had ≤ 1 CAP-associated sign of clinical instability. Signs of CAP-associated instability included systolic blood pressure < 90 mmHg, heart rate > 100 beats per minute, respiratory rate > 24 per minute, arterial oxygen saturation < 90%, or PaO_2 < 60 mmHg on room air. Physicians determined the length of antibiotics in the control group. In both groups, physicians chose the type of antibiotic based on local guidelines. Main outcomes included clinical success rate at days 10 and 30 from hospital admission and CAP-related symptoms at days five and 10 (measured by the 18-item CAP symptoms questionnaire score, range 0-90).

Of the 312 patients who were enrolled, 150 patients were randomized to the control group and 162 to the intervention group. When comparing groups, there were no significant differences in age or sex distribution. The number of days receiving antibiotics was significantly longer for patients in the control group compared to the intervention group (median 10; interquartile range [IQR], 10-11 vs. median 5; IQR, 5-6.5 days, respectively; $P < 0.001$). An intention-to-treat analysis comparing patients at day 10 demonstrated clinical success of 48.6% (71 of 150) in the control group and 56.3% (90 of 162) in the intervention group ($P = 0.33$). There were no differences in clinical success between the control and intervention groups at day 30. At day five and day 10, the mean CAP symptom questionnaire scores were 24.7 (standard deviation [SD], 11.4) vs. 27.2 (SD, 12.5) and 18.6 (SD, 8.5) vs. 17.9 (SD, 7.4), respectively ($P = 0.69$). For the per-protocol analysis, clinical success was 50.4% (67 of 137) in the control group and 59.7% (86 of 146) in the intervention group at day 10 ($P = 0.12$). At day 30, clinical success was 92.7% (126 of 137) in the control group and 94.4% (136 of 146) in the intervention group ($P = 0.54$). At day five and day 10, the mean CAP symptoms questionnaire scores were 24.3 (SD, 11.4) vs. 26.6 (SD, 12.1) and 18.1 (SD, 8.5) vs. 17.6 (SD, 7.4), respectively ($P = 0.81$). The researchers agreed that basing the duration of antibiotic use on clinical stability criteria can be safely implemented in hospitalized patients presenting with CAP.

■ COMMENTARY

Even though CAP is one of the leading causes of morbidity and mortality,[1] the optimal duration of antibiotic treatment for CAP is unknown. For years, it was standard to treat patients until a clinical response occurred. Typically, this resulted in antibiotic length of therapy less than four days.[2] With the growing concern for antibiotic resistance after World War II, doctors increasingly were concerned about relapse of pneumonia and treated for an additional two to three days after resolution of symptoms. Unfortunately, this practice led to the philosophy that treating beyond resolution of symptoms could prevent antibiotic resistance. This mindset translated into common practice until 2007 with the release of the IDSA/ATS guidelines. These guidelines suggested five days of treatment in patients who were afebrile for 48-72 hours and exhibited no signs of clinical instability. Although many entertained these recommendations, they were not widely adopted.

To further investigate the optimal length of antibiotic treatment for CAP and support the IDSA/ATS guidelines, Uranga et al conducted a multicenter, non-inferiority, randomized, clinical trial that included 312 hospitalized patients diagnosed with CAP. At day five, patients were randomized either to an intervention group that limited antibiotics to five days as long as body temperature was ≤ 37.8°C for 48 hours with ≤ 1 CAP-associated sign of clinical instability or to antibiotics per determination of the caring physician. Through these interventions, researchers discovered there was no significant difference in either the clinical success rate or the CAP symptom questionnaire scores. Since this study was a non-inferiority study, its creators did not address specific benefits of shortened length of antibiotic therapy. For instance, the literature says that shortened length of antibiotics leads to lower rates of antibiotic resistance.[3] Reduced duration of antibiotics also may lead to improved adherence, decreased incidence and severity of side effects, and cost savings.[4,5]

Before widely adopting these guidelines, one should be aware of the exclusion criteria that may make this study inapplicable for many patients. These exclusion criteria were extensive and included patients with HIV or chronic immunosuppression (comprising solid organ transplant patients, patients post-splenectomy, taking ≥ 10 mg of prednisone daily or the equivalent for 30 days, on other immunosuppressive agents, demonstrating neutropenia); patients residing in nursing homes; patients discharged from acute care hospitals, onsite subacute care units, or palliative care units within the previous 14 days; and/or patients who had ingested oral antibiotics within 30 days of admission, required longer duration of antibiotics based on cause, required a chest tube, acquired an extrapulmonary infection, or transferred to the ICU prior to randomization. Depending on the site of practice, these exclusion criteria may include the majority of one's patient population. It also may be important to note that 80% of patients received a fluoroquinolone, and it is unclear if these same results would be appreciated with alternative antibiotic regimens.

The IDSA/ATS recommendations for shorter duration of antibiotic treatment based on clinical stability criteria can be safely implemented in hospitalized patients with CAP. It should be noted that these recommendations must be applied safely, ensuring that the exclusion criteria of this study are respected. Future studies are needed to further delineate the benefits of shorter antibiotic courses. ■

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ABSTRACT & COMMENTARY

Listeria Monocytogenes: Maternal-fetal Infection, Bacteremia, and Meningoencephalitis

By Stan Deresinski, MD, FACP, FIDSA

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

SYNOPSIS: Infection with *Listeria monocytogenes* in pregnancy is associated with frequent fetal loss. In others, bacteremia and central nervous system infections are associated with significant mortality.

SOURCE: Charlier C, Perrodeau É, Leclercq A, et al. Clinical features and prognostic factors of listeriosis: The MONALISA national prospective cohort study. *Lancet Infect Dis* 2017 Jan 28. pii: S1473-3099(16)30521-7. doi:10.1016/S1473-3099(16)30521-7. [Epub ahead of print].

Charleir and colleagues prospectively collected data on almost all patients with *Listeria monocytogenes* infection in France during almost four years ending in 2013. Of the 818 patients included in their analysis, 427 had bacteremia, 252 had neurolisteriosis, and 107 had maternal-fetal infection, while the remaining 32 had other forms of infection.

One-third of the 107 women with maternal-fetal infection were from the Maghreb or the Sahel. While the infection usually is symptomatic, the six mothers with late onset listeriosis had normal examinations throughout their pregnancy and delivery. Maternal blood cultures were positive in 47 (55%) of 85 cases, while cultures were positive in 50 (78%) of 64 placental samples and 52 (78) of 67 gastric fluid samples. All pregnant women recovered, including 10 who did not receive antibiotics. Major adverse effects occurred in 89 (83%) cases, including fetal death and

premature delivery at < 32 weeks of gestation. Fetal loss occurred in 26 (24%), with all at < 26 weeks gestation.

[Bacteremia was associated with significantly higher three-month mortality than was central nervous system infection.]

Of the 252 patients with neurolisteriosis, 87% had encephalitis, while the remaining 13 had meningitis alone. Only 42 (17%) had evidence of brainstem involvement and six (2%) had brain abscesses. Cerebrospinal fluid (CSF) was abnormal in all 235 in whom it was examined, with median values of nucleated cells, polymorphonuclear leukocytes, and protein of 457/mm^3, 65%, and 2.1 g/L. The median CSF blood:glucose ratio was 0.31. Only 39% of patients with central nervous system infection survived without neurological impairment.

Bacteremia was associated with significantly higher three-month mortality than was central nervous system infection. Among the independent risk factors for mortality in both bacteremia and neurolisteriosis cases were cancer, pre-existing organ dysfunction, development of multiorgan failure, and monocytopenia. Patients with neurolisteriosis who were bacteremic had higher mortality than those in whom bacteremia was not detected. Among patients with neurolisteriosis, mortality was three times higher in those with encephalitis than those without it. Mortality was higher in patients with central nervous system infection who received dexamethasone. The best outcomes were associated with treatment with an "anti-listeria" ß-lactam (penicillin G, amoxicillin, ticarcillin, piperacillin, imipenem, or meropenem), especially when given with gentamicin. Trimethoprim-sulfamethoxazole also was effective.

An interesting finding was that while CRP was elevated in 96% of the 627 tested, procalcitonin was increased in only 66% of the 186 tested.

■ COMMENTARY

Listeria monocytogenes is an aerobic and facultatively anaerobic, ß-hemolytic, non–spore-forming, short, gram-positive rod with characteristic tumbling motility. On Gram stain, it may be confused with other bacteria, particularly diphtheroids. Among the risk factors for infection are age (neonates and elderly), malignancy, immunosuppressive therapy, alcoholism, diabetes mellitus, chronic liver or renal disease, and iron overload. The incidence of *Listeria* infection per 100,000 population has been reported to be 0.29 overall, 1.3 in individuals ≥ 65 years of age, and 3.0 in pregnant women.

Penicillins and carbapenems are active against *L. monocytogenes*, while cephalosporins are not. The generally recommended treatment is a penicillin with, especially for meningitis, gentamicin, although trimethoprim-sulfamethoxazole alone is also effective. The study reviewed here identified dexamethasone administration as associated with reduced survival.

While encountered infrequently by most clinicians in the United States, it is critical that listeriosis be considered as the cause of febrile illness and, especially, meningitis and encephalitis. ■

ABSTRACT & COMMENTARY

Adult Immunizations — 2017 Changes

By Stan Deresinski, MD, FACP, FIDSA

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

SYNOPSIS: Significant changes in recommendations for adult immunization for 2017 have been made or influenza, meningococcal infection, human papillomavirus, and hepatitis B.

SOURCE: Kim DK, Riley LE, Harriman KH, et al. Advisory Committee on Immunization Practices Recommended Immunization Schedule for Adults Aged 19 Years or Older — United States, 2017. *MMWR Morb Mortal Wkly Rep* 2017;66:136-138.

The Advisory Committee on Immunization Practices (ACIP) has published updated recommendations for immunization of adults. The following is a list of some of the significant changes between the 2016 and 2017 recommendations.

Influenza Vaccine.

• **Live attenuated influenza vaccine (LAIV).** Because of evidence of limited protective efficacy against influenza A(H1N1) pdm09 during the 2013-2014 and 2015-2016 U.S. influenza seasons, LAIV should not be used for the 2016-2017 season.

• Egg allergy.

– Adults who have a history of allergy to eggs but whose only manifestation was the occurrence of hives should receive either inactivated influenza vaccine (IIV) or recombinant vaccine (RV).

– Adults with a history of egg allergy who have had manifestations other than simply hives (e.g., angioedema, respiratory distress, lightheadedness, or recurrent emesis, or who required epinephrine or another emergency medical intervention) may receive age-appropriate IIV or RV, which should be administered in a medical setting with supervision by a healthcare provider with competence in the recognition and management of severe allergic reactions.

Human Papillomavirus Vaccine (HPV).

• Previously unvaccinated (0 doses) adult females and adult males (through 26 years and 21 years of age, respectively) should receive three doses of HPV at 0, 1-2, and 6 months.

• Previously unvaccinated (0 doses) adult males ages 22 through 26 years may receive three doses of HPV at 0, 1-2, and 6 months.

• Adult females through age 26 years and adult males through age 21 years (as well as males ages 22 through 26 years who may receive HPV vaccine) who initiated the HPV vaccination series before age 15 years and received two doses at least five months apart are considered adequately vaccinated and do not need an additional dose of HPV vaccine.

• Adult females through age 26 years and adult males through age 21 years (and males ages 22 through 26 years who may receive HPV vaccine) who initiated the HPV vaccination series before age 15 years and received only one dose, or two doses less than five months apart, are not considered adequately vaccinated and should receive one additional dose of HPV vaccine.

Meningococcal Vaccine.

• Adults with anatomical or functional asplenia or persistent complement component deficiencies [this includes receipt of eculizumab] should receive:

- A two-dose primary series of serogroups A, C, W, and Y meningococcal conjugate vaccine (MenACWY), with doses administered at least two months apart, and should be revaccinated every five years AND

- Serogroup B meningococcal vaccine (MenB) with either MenB-4C (two doses administered at least one month apart) or MenB-FHbp (three doses administered at 0, 1-2, and 6 months).

• HIV-infected adults should receive:

- If previously unvaccinated, a two-dose primary MenACWY vaccination series, with doses administered at least two months apart, and should be revaccinated every five years.

- If previously received one dose of MenACWY, a second dose at least two months after the first dose.

- Note: MenB is not routinely recommended for adults with HIV infection, because meningococcal disease in this population is caused primarily by serogroups C, W, and Y.

• Microbiologists potentially routinely exposed to isolates of *Neisseria meningitidis* should receive one dose of MenACWY and should be revaccinated every five years if the risk for infection remains, as well as either MenB-4C (two doses administered at least one month apart) or MenB-FHbp (three doses administered at 0, 1-2, and 6 months).

• Adults at risk because of a meningococcal disease outbreak should receive one dose of MenACWY if the outbreak is attributable to serogroup A, C, W, or Y; or, if the outbreak is attributable to serogroup B, either MenB-4C (two doses administered at least one month apart) or MenB-FHbp (three doses administered at 0, 1-2, and 6 months).

• Young adults at risk ages 16 through 23 years (preferred age range is 16 through 18 years) who are healthy and not at increased risk for serogroup B meningococcal disease may receive either MenB-4C (two doses administered at least one month apart) or MenB-FHbp (three doses administered at 0, 1-2, and 6 months) for short-term protection against most

strains of serogroup B meningococcal disease.

Hepatitis B Vaccine.
• Adults with chronic liver disease, including, but not limited to, hepatitis C virus infection, cirrhosis, fatty liver disease, alcoholic liver disease, autoimmune hepatitis, and an alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level greater than twice the upper limit of normal should receive a HepB series. ■

Updates

By Carol A. Kemper, MD, FACP

Ebola Preparedness in Hospitals

SOURCE: Cummings KJ, Choi MJ, Esswein EJ, et al. Addressing infection prevention and control in the first U.S. community hospital to care for patients with Ebola virus disease: Context for national recommendations and future strategies. *Ann Intern Med* 2016;165:41-49.

During the next five years, the federal government will provide $12 million in funding to three institutions in the United States (Emory University, University of Nebraska Medical Center, and Bellevue Hospital Center) to co-lead the National Ebola Training and Education Center. This collaborative effort is intended to support training and education of U.S. hospital healthcare personnel in the management of high-level infectious diseases, such as Ebola. Previously, Emory and Nebraska Medical Center had worked in conjunction with the Centers for Disease Control and Prevention (CDC) to educate and train more than 460 healthcare personnel at 87 facilities.

Training efforts will focus on: the prompt recognition and isolation of at-risk patients with immediate use of appropriate personal protective equipment (PPE); basic PPE education and training; standardization of signage between facilities related to isolation procedures and PPE; and development of a "system-wide" inter-disciplinary group to address emerging infectious threats. In addition, they plan to expand high-level PPE training to all employees in the emergency department, inpatient care units, MICU, and labor and delivery at the above facilities. The CDC also has formed an "Ebola response team," which can be deployed anywhere in the United States for a highly suspicious or confirmed case.

Other new national recommendations and policies for addressing emerging infectious diseases for hospital personnel include:
• Annual training and refresher course for basic PPE;
• Annual education on high-level PPE and respirator use with supervision by trained personnel;
• Annual training and competencies for high-level PPE with donning and doffing;
• Consideration of conducting one clinical disaster drill annually.

[Although drills are costly and take personnel away from day-to-day tasks, there are numerous benefits to conducting clinical disaster drills.]

Although drills are costly and take personnel away from day-to-day tasks, there are numerous benefits to conducting clinical disaster drills. At our facility, repeated drills and education gave hospital staff a sense of control and comfort during the Ebola threat of 2014-2015. Although the chances that our facility would be affected were extremely low, it was challenging to enlist the support of some employees, and some of the nursing staff were so terrified they literally quit their jobs. Within six months, we conducted 25 drills for hospital personnel, including all staff potentially affected, followed by open debriefing sessions with the CMO, infectious disease, and infection control personnel. Not only did this allow us to identify gaps in our procedures and tighten up the plan, but it engaged people in open conversation, encouraged everyone to participate and express their concerns and ask questions, and went a long way toward allaying fear. It also engendered camaraderie among all levels of staff, and inspired everyone's involvement in a way that made everyone feel they had something important to contribute. And I thought all that practice for Ebola responsiveness made the hospital run more smoothly in the following months.

Meningococcal Vaccine Recommended for HIV+ Persons

SOURCE: MacNeil JR, Rubin LG, Patton M, et al. Recommendations for use of meningococcal conjugate vaccines in HIV-infected persons — Advisory Committee on Immunization Practices, 2016. *MMWR Morb Mortal Wkly Rep* 2016;65: 1189-1194.

As of Nov. 4, 2016, all HIV-infected persons 2 years of age and older should receive two doses of conjugate meningococcal ACWY vaccine (MenACWY-D [Menactra, Sanofi Pasteur] or MenACWY-CRM [Menveo, GlaxoSmithKline]), at least two months apart, with revaccination every five years. HIV-infected persons 56 years of age and older (for whom these vaccines are not routinely recommended nor FDA approved if not HIV-infected) are included in this recommendation. Persons who previously received one dose of meningococcal conjugate vaccine should receive a booster dose using the same vaccine when known.

Mandatory reporting requirements for meningococcal infection do not require information on HIV status, even when known, so the true incidence of meningococcal infection in HIV-infected persons is not known. During the past few years, the occurrence of several outbreaks of meningococcal infection within groups of men who have sex with men (MSM), many of whom were HIV-infected, has prompted much discussion about whether HIV-infected persons are at increased risk for meningococcus and the risks/benefits of vaccination in this group of individuals.

By now, the evidence is sufficiently compelling — HIV-infected persons do appear to be at increased risk for meningococcal infection. From 1995-2014, nearly 4,000 cases of meningococcal disease were reported through the National Notifiable Diseases Surveillance System. Sixty-two (2%) of these were known to be HIV-infected, the majority of whom were adults 20-59 years of age. Of these, 69% were due to serogroup ACWY, 21% to serogroup B, and 10% were not known or other. While recent observations from New York and the United Kingdom did not suggest an increased mortality in HIV-infected persons when infected with meningococcus, data from South Africa did observe an increased risk of death in HIV-infected persons with meningococcus compared with non-HIV infected persons (20% vs. 11%, respectively).

HIV providers should be aware that the immunogenicity of meningococcal vaccine improves with increasing CD4 count, and those with lower CD4 counts may have a poor response to vaccine. One recent study measured seroresponses in adult HIV-infected persons to one or two doses of MenACWY-D vaccine, as defined by either a four-fold rise in titer or a titer ≥ 1:128 using a rabbit complement bactericidal assay. In those with a CD4 count percentage ≥ 15%, seroresponses to serogroup C at 4, 28, and 72 weeks following a single dose of vaccine were 65%, 31%, and 21%. In those with CD4 counts ≥ 15% who received two doses of vaccine six months apart, seroresponses to serogroup C following the second dose were marginally improved at 59%, 64%, and 35%. However, in those with lower CD4 counts, all of whom received two doses of vaccine six months apart, responses to serogroup C were only 22%, 22%, and 6%. Seroresponses to serogroup Y were somewhat better than to serogroup C. Severe side effects were followed for six weeks post-vaccination and occurred in 2.2% to 6.5%. Seroresponses in HIV-infected children were somewhat better than in HIV+ adults.

Recommendations for meningococcal vaccine over the past few years have been evolving quickly. As of November 2016, current recommendations for routine vaccination with MenACWY in the United States include:

- all healthy adolescents;
- all persons with HIV-infection ≥ 2 years of age (including those ≥ 56 years of age);
- all persons ≥ 2 months with certain medical conditions (genetic deficiencies of complement pathway, persons receiving eculizumab, and persons with functional or anatomic asplenia, including those with sickle cell disease);
- microbiologists routinely at increased risk for exposure to meningococcal isolates;
- military recruits;
- first-year college students planning to reside in residence halls;
- persons who travel or reside in areas where meningococcus is hyperendemic (e.g., Hajj);
- persons at increased risk during an outbreak of meningococcus ACWY.

Recommendations for routine vaccination with serogroup B vaccine now include:

- those with persistent complement deficiencies;
- those with functional or anatomic asplenia;
- microbiologists (as above);
- those affected by an outbreak of meningococcus B.

For details, see the recent 2016 ACIP adult immunization schedule (www.cdc.gov/vaccines/schedules/hcp/adult.html). ■

CME INSTRUCTIONS

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CME QUESTIONS

1. Tonsillectomy is associated with which of the following?

a. Reduced infection in the first post-operative year when done for recurrent throat infections

b. Reduced school absence in the first post-operative year when done for recurrent throat infections

c. No persistent improvement in infections and school absence after the first post-operative year

d. Improved sleep outcomes in the first post-operative year when done for sleep-disordered breathing

e. All of the above

2. Which of the following is *not* correct with regard to the results of the study by Navlekele et al?

a. The median time of onset of acute kidney injury after initiation of therapy with piperacillin/tazobactam plus vancomycin was day 3.

b. The median time of onset of acute kidney injury after initiation of therapy with cefepime plus vancomycin was day 5.

c. Median trough vancomycin levels were similar in patients receiving piperacillin/tazobactam plus vancomycin and those receiving cefepime/vancomycin.

d. Treatment with piperacillin/tazobactam plus vancomycin is associated with a lower risk of acute kidney injury than is treatment with cefepime plus vancomycin.

3. Which of the following is appropriate with regard to influenza vaccination of patients with a history of hives after previous influenza vaccination for the 2016-2017 season?

a. The patient should not receive any influenza vaccine.

b. The patient should receive the live attenuated influenza vaccine (LAIV).

c. The patient should receive either inactivated influenza vaccine or recombinant influenza vaccine.

d. The patient may receive recombinant influenza vaccine but not inactivated influenza vaccine.

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.