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Infectious Disease [ALERT]

Incisive Commentary and Clinical Abstracts on Current Issues in Infectious Diseases

ABSTRACT & COMMENTARY

Vaping and Severe Acute Pneumonitis

By Stan Deresinski, MD, FACP, FIDSA

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

SYNOPSIS: As of Aug. 27, 2019, 215 cases of severe pulmonary disease possibly related to vaping have been reported to the CDC. Evidence to date suggests the illness is a form of acute lipoid pneumonia likely related to inhalation of lipid materials.

SOURCES: Davidson K, Brancato A, Heetderks P, et al. Outbreak of electronic-cigarette–associated acute lipoid pneumonia — North Carolina, July-August 2019. *MMWR Morb Mortal Wkly Rep.* ePub: 6 September 2019.

Schier JG, Meiman JG, Layden J, et al. Severe pulmonary disease associated with electronic-cigarette–product use — interim guidance. *MMWR Morb Mortal Wkly Rep*. ePub: 6 September 2019. DOI: http://dx.doi.org/10.15585/mmwr.mm6836e2external icon.

Five patients presented to two North Carolina hospitals in July and August 2019 with severe pneumonitis that progressed to hypoxemic respiratory failure. Each had been "vaping," using vaping pens and/or electronic cigarettes with refillable chambers or interchangeable cartridges filled with tetrahydrocannabinol concentrates or oil that had been purchased "on the street."

The patients complained of worsening dyspnea, nausea, vomiting, abdominal discomfort, and fever, and both exhibited peripheral blood neutrophil-predominant leukocytosis. They received empiric antibiotics recommended for treatment of community-acquired pneumonia, but tests for microbiological etiologies proved negative. Chest computerized tomography revealed infiltrates that were mostly basilar with ground glass opacities and tree-in-bud patterns. While no microbial etiology was identified on evaluation of bronchoalveolar lavage fluid, staining of cytological specimens with Oil Red O allowed visualization of lipid-laden macrophages. Rapid clinical improvement occurred after administration of methylprednisolone, and

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only one patient required intubation and mechanical ventilation. All five survived.

These cases are among the wave of reported cases of severe pulmonary disease associated with electronic cigarette product use in the United States; more than 380 cases were reported by 36 states and one U.S. territory as of Sept. 12, 2019. The clinical presentation and course of these cases appear to be generally compatible with that of the five North Carolina cases described above, but at least seven patients have died. Lipid-laden macrophages from cytological specimens also have been identified in a number (but not all) of these cases, contributing to the belief that the illness represents a form of exogenous lipoid pneumonia. In addition, many patients appear to have responded similarly to corticosteroid therapy.

■ COMMENTARY

Electronic cigarette devices produce an aerosol that may contain a variety of chemicals depending on what is placed in the chamber, such as nicotine or THC and associated oils, but also other substances. The finding of lipid-laden macrophages on cytological specimens from the respiratory tract of several cases, together with an inability to identify an infectious etiology, is compatible with a diagnosis of lipoid pneumonia resulting from inhalation of lipids.

Most cases of exogenous lipoid pneumonia, which, at least in its chronic form is considered to result from a foreign body reaction to fat, have an insidious onset and chronic course, unlike that seen in the cases discussed here. However, the potential for massive inhalation with the use of vaping devices could account for the more acute presentations of the current cases. The inhaled lipid possibly responsible for this illness remains uncertain, but one, vitamin E acetate, has been identified in many but not all vaping samples from cases tested so far.

The CDC now warns that, until the definitive cause of these illnesses is determined, "persons should consider not using e-cigarette products" and that, independent of this continuing investigation, electronic cigarette users should not acquire these products off the street and should not modify or add substances not intended by the manufacturer to any product. The CDC also states the following: "E-cigarette products should never be used by youths, young adults, pregnant women, or by adults who do not currently use tobacco products. Adult smokers who are attempting to quit should use evidence-based smoking cessation treatments, including counseling and FDA-approved medications; those who need help quitting tobacco products, including e-cigarettes, should contact their medical provider. Persons who are concerned about harmful effects from e-cigarette products may call their local poison control center at 1-800-222-1222." ■

ABSTRACT & COMMENTARY

Urinary Tract Infection With Bacteremia in Young Infants: Duration of Parenteral Therapy

By Philip R. Fischer, MD, DTM&H

Professor of Pediatrics, Department of Pediatric and Adolescent Medicine, Mayo Clinic, Rochester, MN

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

SYNOPSIS: The duration of parenteral antimicrobial therapy for bacteremic urinary tract infection in young infants varies between practitioners and centers. A retrospective review suggests that extending parenteral treatment beyond seven days does not alter outcomes.

SOURCE: Desai S, Aronson PL, Shabanova V, et al; Febrile Young Infant Research Collaborative. Parenteral antibiotic therapy duration in young infants with bacteremic urinary tract infections. *Pediatrics* 2019;144:e20183844.

The urinary tract is one of the most common sites of bacterial infection in babies younger than 2 months of age, and approximately 10% of these young infants with urinary tract infection have concurrent bacteremia. Despite the relative frequency and importance of these infections, there is not a widely accepted standard duration of initial parenteral therapy. Although longer courses are known to be effective in reducing mortality and morbidity due to the initial infection, prolonged antibiotic therapy can be expensive and carries a risk of secondary infection and blood clots associated with the use of intravenous lines. Thus, Desai and colleagues sought to compare outcomes in children who were treated with shorter courses of parenteral therapy with those who received longer courses.

The study included infants ages 0 to 60 days who were evaluated for possible invasive bacterial infection at 11 geographically diverse children's hospital emergency departments from July 2011 through June 2016 and who were found to have bacteremia and a urinary tract infection (with the same bacteria identified in both the blood and urine). Children who also had concurrent focal infection (meningitis or septic arthritis, for instance) were excluded from the study. The median duration of parenteral antibiotic treatment was seven days, so researchers compared those who received seven or fewer days of parenteral treatment (short course) and those who received more than seven days of parenteral treatment (long course).

The study included 115 patients. Half were younger than 1 month of age, and 60% were male. Overall, 9% of the included study subjects had been born prematurely, and 17% had a complex chronic medical condition. Fever was a presenting finding in 89% of the infected babies. *Escherichia coli* was the most common etiologic agent identified, accounting for 81% of infections. None of the causative bacteria was an extended spectrum beta-lactamase producing organism. There was in vitro evidence that each infecting bacteria could have been susceptible to an oral antibiotic.

Half of the included patients received seven or fewer days of parenteral therapy, and half of the patients received seven, 10, or 14 days of therapy (presumably corresponding to established protocols). Great variation in the duration of treatment occurred among the 11 centers participating in the study. Centers varied from 11% to 81% receiving "short" courses of parenteral antibiotics. Children who appeared to be ill on presentation and children with non-*E. coli* infections tended to be treated with longer courses of parenteral antibiotics.

Six infants had a recurrent urinary tract infection 15 to 30 days after the initial hospital discharge. Two of them had received short-course parenteral antibiotics and four had received long-course parenteral antibiotics. In two of the children with recurrent infection who had received long-course parenteral antibiotics, a different germ caused the second infection. Overall, 13% of the babies required medical care within the month after the initial urinary tract infection; this rate was similar between short- and long-course treatment groups.

Interestingly, prescribing providers opted for short-course treatment in 60% of the 67 babies who appeared well and had no underlying chronic medical condition. Longer-course treatment outcomes were no better than shorter-course treatment outcomes in this "healthy" subset of patients.

[Despite a variety of diagnostic schemes and despite lots of outcome data, there still is not a clear consensus about how best to handle young infants with fever.]

The authors noted that shorter-course treatment was associated with shorter hospital stays (4.5 vs. 10.8 days) but not with any other different outcome (recurrent infection or subsequent use of healthcare resources). They acknowledged that their study did not include a review of oral antibiotic treatment after the initial parenteral course.

■ COMMENTARY

Over recent decades, there has been widespread recognition of the importance of appropriately diagnosing and managing young infants with fever. Despite a variety of diagnostic schemes (with newer biomarkers emerging) and despite lots of outcome data, there still is not a clear consensus about how best to handle young infants with fever. Part of the challenge comes from trying to avoid the small risk of death from missed diagnoses and inadequate treatments with the seemingly less onerous risks

of prolonged hospital stays, increased costs, and nonfatal complications of treatment. Desai and colleagues used the natural experiment of varying practice patterns to show clearly that longer-course treatment was associated with increased lengths of stay (and, presumably, cost) without adding any measurable reduction in the risk of poor outcomes. One could speculate that the two babies who had subsequent urinary tract infections from different bacteria after their initial longer course of parenteral treatment might have been predisposed to the development of new or resistant infection by that longer course of treatment.

Of course, skeptics could claim that the researchers only included 115 children. Pediatricians frequently subject febrile newborns to parenteral antibiotics for 24-48 hours while awaiting negative cultures to confirm the lack of bacterial infection and realizing that no more than a small percent of those febrile babies has a serious bacterial infection. Proponents of longer-course parenteral antibiotic therapy still could believe that they are preventing bad outcomes in the half percent or so of babies who would have been missed by this small study. Non-skeptics will point out that no children were helped by longer-course parenteral antibiotics over the five years of the study in 11 different pediatric centers — making the benefit hidden by the size of the study to be very, very small.

How should clinicians respond to these data? Certainly, those working at institutions that mandate or encourage longer intravenous courses of antibiotics for bacteremic urinary tract infection in young infants should reconsider their policies. All practitioners should feel free to consider limiting parenteral therapy to no more than seven days, especially when managing a baby who appears otherwise well without underlying medical conditions. Also, further research should be done; it is possible that even seven days is longer than needed to treat infected newborns adequately. ■

ABSTRACT & COMMENTARY

Febrile Urinary Tract Infection in Young Infants — Value of Spinal Fluid Analysis

By Philip R. Fischer, MD, DTM&H

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

SYNOPSIS: Practices vary significantly as clinicians evaluate and manage febrile infants younger than 2 months of age. A retrospective review suggests that meningitis is extremely unlikely in well-appearing babies with initial laboratory results suggestive of urinary tract infection, and that cerebrospinal fluid analysis may not be necessary.

SOURCE: Wang ME, Biondi EA, McCulloh RJ, et al. Testing for meningitis in febrile well-appearing young infants with a positive urinalysis. *Pediatrics* 2019;144:e20183979.

Fever is a common presenting symptom in young infants, and urinary tract infection is the most likely serious bacterial infection in this group. Various criteria have been established to guide appropriate evaluation and management of febrile babies, but clinical practices still vary widely. Specifically, there has been controversy about the value of cerebrospinal fluid testing in febrile but otherwise well-appearing babies during the second month of life, especially when initial testing suggests that a urinary tract infection is the (or a) cause of the fever. Choosing not to look for meningitis in these babies carries the risk of under-treating a central nervous system infection and leaving the baby with lasting adverse outcomes. However, there are risks to conducting "excessive" diagnostic testing, and the actual risk of meningitis co-occurring with urinary tract infection during the first months of life is unknown.

Thus, Wang and colleagues performed a secondary analysis of data within the Reducing Excessive Variability in Infant Sepsis Evaluation quality improvement project that is led by a network associated with the American Academy of Pediatrics. Overall, the study group's goal is to increase the rate of appropriate evaluation and care for well-appearing infants ages 7 to 60 days who present with fever. This is an observational study, and the collection of spinal fluid samples was left

to treating clinicians and was not mandated by the study group. A total of 124 hospitals participated in the study, including both academic and community institutions.

Patients who appeared "toxic," "ill," "sick," or "lethargic" were not included in the study. Patients with underlying chronic conditions that might alter the risk of bacterial infection and children with obvious bronchiolitis were excluded. Thus, included patients were previously well and looked well (other than having fever) and did not have an obvious site of infection prior to laboratory analysis.

Included patients were classified by age (7-30 days vs. 31-60 days), evidence of probable urinary tract infection (white blood cells, nitrite, or leukocyte esterase at higher than normal levels in the urine), and the presence or absence of inflammatory markers (abnormal white blood cell count, C-reactive protein level, or procalcitonin level). Collected data also included whether the physician had treated a urinary tract infection or meningitis based on microbial growth on sampled fluids.

During the two years of the study, 20,570 well-appearing febrile infants 7-60 days of age were included in the study. Of these, 89% underwent a urinalysis prior to decisions about hospital admission or dismissal from the emergency department; 19% of the urinalyses were consistent with the likelihood of a urinary tract infection. Of those patients with presumed urinary tract infection, 70% underwent spinal fluid analysis (vs. 58% of those without an abnormal urine test). Of those with abnormal urinalyses, the younger patients (first month of life), males, and those with abnormal inflammatory markers were more likely to have cerebrospinal fluid testing.

The rate of spinal fluid testing varied significantly by study site. For children in the first month of life with abnormal urinalyses, rates of spinal fluid analysis varied by institution from 64% to 100%. For children in the second month of life with abnormal urinalyses, rates of spinal fluid analysis varied from 10% to 100%. Hospitals with the highest number of febrile infants were most likely to conduct spinal fluid testing.

There were 1,061 infants with a positive urinalysis who did not have spinal fluid evaluation. Of these, 734 received empiric antibiotics, and 505 received a full course of antibiotics designed to treat urinary tract infection. (The selection and dosing of antibiotics vary in babies with urinary tract infection vs. meningitis.) Of all the patients who did not have spinal fluid testing, none subsequently developed meningitis.

The authors summarized by noting that, for well-appearing febrile babies who had abnormal urinalyses, there was a wide variation in practices for performing tests to rule out concurrent meningitis. Spinal fluid testing was most common for babies younger than 1 month of age, for those with abnormal inflammatory markers, and for those seen at high-volume pediatric centers. However, 30% of febrile young infants still did not receive spinal fluid testing, and none of the non-tested babies had adverse outcomes. It seems that cerebrospinal fluid analysis might not be as necessary as some practitioners think.

[For well-appearing febrile babies who had abnormal urinalyses, there was a wide variation in practices for performing tests to rule out concurrent meningitis.]

■ COMMENTARY

The United States spends relatively more money on medical care than many other countries. Some think that this is because of an excessive reliance on expensive testing (instead of using clinical judgment) and because of a fear of missing rare possibilities. Indeed, there is a tension between settling for a near-certain diagnosis and ruling out less likely dangerous diagnoses. The authors of this new paper suggest that perhaps some of the current testing of otherwise well-appearing febrile young infants is not necessary. With significant practice variations, whether spinal fluid analysis was done for well-appearing febrile babies with evidence of a urinary tract infection was not associated with missed diagnoses of meningitis.

Of course, meningitis can co-occur with urinary tract infections. Children who appear ill and children who have underlying medical conditions would be less likely to forgo spinal fluid testing when febrile as young infants. However, otherwise healthy young infants who, other than being febrile, appear well and have abnormal urinalyses should be able to be treated safely for the urinary tract infection without conducting additional testing to rule out meningitis. ■

ABSTRACT & COMMENTARY

Spotted Fever Rickettsioses and Meningoencephalitis

By Dean L. Winslow, MD, FACP, FIDSA

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

SYNOPSIS: Researchers reviewed 19 cases of meningoencephalitis associated with spotted fever rickettsioses. Fever was present in all cases. Rash was present in 100% of pediatric patients but in only 50% of adult patients. Cerebrospinal fluide pleocytosis was present in 88% of patients. Ninety percent of patients required ICU admission, and only 46% of patients recovered completely.

SOURCE: Bradshaw MJ, Carpenter Byrge K, Ivey KS, et al. Meningoencephalitis due to spotted fever rickettsioses, including Rocky Mountain spotted fever. *Clin Infect Dis* 2019; doi:10.1093/cid/ciz776. [Epub ahead of print].

Nineteen patients (11 children and eight adults) met the criteria for spotted fever rickettsioses encephalitis. Patients were identified through hospital laboratory-based surveillance or through the Tennessee Unexplained Encephalitis Study. Chart reviews were conducted for cases that met inclusion criteria; when available, independent reviews of the neuroimaging were performed.

Rash was significantly more common in children than in adults (100% vs. 50%), but other clinical features were similar between the two groups. One-third of patients had no history of tick exposure. Cerebrospinal fluid (CSF) pleocytosis and protein elevation each were present in 87.5% of cases; hypoglycorrhachia was found in 18.8% of cases. Leukocytosis and mild thrombocytopenia were common.

[Considering rickettsial disease is particularly important in febrile patients with or without meningoencephalitis, even in patients without a history of a tick bite and in those without a rash.]

Mild elevations of serum transaminases were present in all but one case. CSF pleocytosis was mild (median 41 cells/μL), and neutrophil predominance was present in one-third of cases. Median CSF protein was 83 mg/dL, and mild hypoglycorrhachia was seen in a few cases. The starry sky sign (multifocal, punctate diffusion restricting or T2 hyperintense lesions) was noted on MRI in all children, but it was not seen in any adult patients.

Ninety percent of patients required ICU admission, and 39% were intubated. The outcomes were similar between adults and children, with only 46% of patients making a complete recovery by discharge. Late deaths due to disease occurred, and many patients who survived were left with significant residual neurological deficits.

■ COMMENTARY

This is a very important paper that reminds clinicians to always consider rickettsial infection in the differential diagnosis of meningoencephalitis in areas where rickettsioses are common, and especially in febrile patients during the warmer months. Considering rickettsial disease is particularly important in febrile patients with or without meningoencephalitis, even in patients without a history of a tick bite and in those without a rash. Doxycycline should be started empirically in both adults and children with febrile illnesses who are at risk for rickettsial disease. (Doxycycline is a relatively weak chelating agent compared to older tetracyclines and, with short courses, it is unlikely to cause dental discoloration in children.) Importantly, serology can be negative at initial presentation. Confirmation of diagnosis often can be made by repeating convalescent serology at two weeks.

Although the patients reported in this case series may have been sicker than those with Rocky Mountain spotted fever without clinical evidence of encephalitis,

it is also telling that doxycycline was not initiated until seven to eight days after the onset of fever in these patients, and likely contributed to the poor outcome. Interestingly, pediatricians started empiric doxycycline on the day of admission in all of their patients. However, adult patients in this study did not receive doxycycline until a median of three days after admission. ■

ABSTRACT & COMMENTARY

Cigarette Smoke Increases the Virulence of *Staphylococcus aureus*

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

SYNOPSIS: In an experimental study, investigators found cigarette smoke increases the virulence of *Staphylococcus aureus* strains through several mechanisms, including augmented biofilm formation, increased invasion ability, and persistence within bronchial alveolar cells.

SOURCE: Lacoma A, Edwards AM, Young BC, et al. Cigarette smoke exposure redirects *Staphylococcus aureus* to a virulence profile associated with persistent infection. *Sci Rep* 2019;9:10798.

Cigarette smoking has a multitude of detrimental effects on human health, including an increased risk for certain infections such as pneumonia. The mechanisms underlying the increased risk are not fully elucidated, but they are thought to involve dysregulation of host immunity and damage to the integrity of the respiratory epithelium. Previous epidemiological studies have suggested an association between cigarette smoking and *Staphylococcus aureus* prevalence. Therefore, Lacoma and colleagues sought to assess the effects of cigarette smoke (CS) on specific virulence mechanisms important in the pathogenesis of *S. aureus*.

The study involved several in vitro experiments that used clinically significant lineages of methicillin-susceptible *S. aureus* (MSSA) and methicillin-resistant *S. aureus* (MRSA). CS was extracted and combined with tryptic soy broth (CS-TSB), which then was used to inoculate MRSA and MSSA cultures. The researchers then assessed biofilm formation, cytotoxicity, cell invasion and persistence, mutational frequency, and whole genome sequencing.

The investigators discovered that community-associated MRSA strains survived better within CS-TSB than hospital-associated MRSA strains. Inactivation of the accessory gene regulator (Agr), which is a global virulence regulator, had no effect on growth in CS-TSB. CS promoted biofilm formation, which was associated with decreased Agr activity. Growth in CS-TSB led to significantly decreased toxin production that corresponded to CS-mediated downregulation of Agr, although the extent of toxin decrease varied among the *S. aureus* strains. Furthermore, four strains grown in CS-TSB, but not regular TSB, demonstrated an increased invasive capacity in bronchial epithelial cells. Growth in CS-TSB also increased the population frequency of gentamicin-resistant small colony variants (SCVs) and rifampicin-resistant SCVs. Additional investigation of this mechanism determined that CS exposure increased the number of mutations in all of the tested strains, and reactive oxygen species within CS were major triggers for gentamicin-resistant SCVs. Interestingly, purified nicotine had no significant effect on SCV emergence. CS also affected cell wall teichoic acids (TAs), which play an important role in maintaining the cell wall of *S. aureus*. A TA mutant was highly sensitive to CS-TSB, suggesting that TAs mediate resistance to CS inhibition. Finally, when the growth media used for the SCVs was changed back to regular TSB, the majority of the colonies rapidly reverted back to wild-type.

■ COMMENTARY

This study elegantly describes the myriad changes that CS induces in *S. aureus*. The investigators found both the degree of CS exposure and the genetic background of the *S. aureus* strains are important in determining the effects of CS. This likely explains why some previous studies found CS to be a risk factor for *S. aureus* colonization, whereas others did not. For example, differences in the expression

of teichoic acids in MRSA might be an important prerequisite for MRSA colonization in smokers. Furthermore, the observed resistance to gentamicin and rifampicin in the presence of CS also might affect other antibiotics, such as fluoroquinolones, for which resistance occurs through target site mutations.

[Smoking can be viewed as a modifiable risk factor that is especially important for patients with recurrent *S. aureus* infections.]

In chronic rhinosinusitis, cigarette smoking has been identified as a significant risk factor, along with *S. aureus* SCVs. The findings from the present study provide a plausible explanation for recalcitrant disease, whereby CS induces the formation of SCVs leading to *S. aureus* colonization and resistance to antibiotic therapy. Notably, recent data have shown that CS induces double-stranded DNA damage in human cells in vivo. CS likely also causes similar damage to *S. aureus* DNA, leading to mutations and SCV emergence. Further in vitro and in vivo studies are warranted to test this hypothesis.

The study has a few limitations. For one, brief exposure to CS in vitro is unlikely to be equivalent to inhaled smoke over prolonged time periods. Another is that many other factors are involved with *S. aureus* colonization, which makes determining the role of confounding variables a challenge. It also would have been interesting to know if CS influenced the development of SCVs that were resistant to common drugs used for MRSA, such as doxycycline and trimethoprim-sulfamethoxazole.

Lacoma and colleagues provide valuable evidence of the deleterious effects of CS on *S. aureus*, which can be useful to clinicians when they are counseling patients to stop smoking. Therefore, smoking can be viewed as a modifiable risk factor that is especially important for patients with recurrent *S. aureus* infections, such as abscesses or rhinosinusitis. Smokers should be reminded that the best time to quit smoking was the day they started; the second best time to quit is today. ■

ABSTRACT & COMMENTARY

Acute Kidney Injury With Combination Antibiotics in the Critically Ill

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

SYNOPSIS: In this retrospective study, a short course (24 to < 72 hours) of combination antibiotic therapy with piperacillin-tazobactam and vancomycin was not associated with an increased risk of acute kidney injury among critically ill patients when compared with other β-lactam and vancomycin combinations.

SOURCE: Schreier DJ, Kashani KB, Sakhuja A, et al. Incidence of acute kidney injury among critically ill patients with brief empiric use of antipseudomonal β-lactams with vancomycin. *Clin Infect Dis* 2019;68:1456-1462.

In this retrospective study, the authors attempted to define the incidence of acute kidney injury (AKI) with a short course (at least 24 but less than 72 hours of therapy) of β-lactam and vancomycin combination therapy in the critically ill. AKI was defined by the Acute Kidney Injury Network (AKIN) criteria based on both urine output and serum creatinine (SCr). The three antibiotic combinations assessed for outcomes were piperacillin-tazobactam/vancomycin (PTZ/VAN), cefepime/vancomycin (CEF/VAN), and meropenem/vancomycin (MER/VAN).

The authors created an electronic alert that continuously "sniffed" the medical record for changes in either urine output or baseline serum creatinine. Baseline SCr was defined as the median of all creatinine values in the preceding six months prior to the index admission during which exposure to the β-lactam/vancomycin combination occurred. The authors manually confirmed AKI when a "sniff" (i.e., electronic alert) popped up. The primary endpoint for the purpose of analysis was the incidence of AKI (stage 2 or 3). Secondary

endpoints included maximal stage AKI and a composite of major kidney events 60 days after the start of therapy ($MAKE_{60}$), consisting of a new need for renal replacement therapy (RRT), persistent doubling of serum creatinine at 60 days, or death. Researchers reviewed 5,791 patient records (regardless of ICU type) and they used 3,299 patient data sets for analysis. Exclusion criteria included use of more than one antipseudomonal drug, recent use of combination antibiotic therapy, presence of stage 2 or 3 AKI at baseline, or death within 48 hours of the start of therapy. Patients with end-stage renal disease also were excluded.

AKI incidence was assessed beginning 24 hours after the start of continuous concurrent therapy with one of the three antibiotic combination groups (PTZ/VAN, CEF/VAN, or MER/VAN). Logistic regression models were fit using AKI as the outcome variable and the three combination therapies as independent variables. One model was fit using a validated AKI risk score as a predictor variable that assigns points for chronic conditions, acute conditions, and nephrotoxin exposure in the intensive care unit. The second model used all patient and treatment variables as predictors thought to affect AKI risk.

All three combination antibiotic groups had similar characteristics at baseline, although the MER/VAN group had a slightly greater frequency of acidosis, anemia, sepsis, and need for mechanical ventilation. The overall incidence of any stage AKI was 34%, with most developing stage 1 AKI (26%). With unadjusted analysis, no increased risk of AKI stage 2 or 3 was found with short courses of PTZ/VAN when compared to short courses of CEF/VAN or MER/VAN. Similarly, the antibiotic group was not associated with an increased risk of stage 2 or 3 AKI in the multivariable models adjusting for baseline AKI risk.

The authors performed stratified analyses according to the presence or absence of stage 1 AKI at initiation of antibiotic therapy and similarly found no increased risk of stage 2 or 3 AKI development with any of the three combination antibiotic regimens. A numerically higher incidence of AKI stage 1 was noted in patients treated with PTZ/VAN relative to other groups, but was attributed to competitive inhibition of secretion of creatinine by piperacillin. With respect to the $MAKE_{60}$ composite endpoint, there were no differences between groups. When stratified by $MAKE_{60}$ subsets, there was an increased risk of death in the MER/VAN group, reflecting higher baseline disease severity.

■ COMMENTARY

Previous studies have raised concerns about combination antibiotic therapy and AKI risk, but they did not exclusively study critically ill patients and/or were meta-analyses of small, heterogeneous studies.[1,2] A single-center, retrospective study that compared rates of AKI among critically ill patients receiving combination therapy (PTZ/VAN, CEF/VAN, or MER/VAN) showed increased odds of AKI using PTZ/VAN compared to the other groups.[3] The groups were well-matched except most patients were in surgical intensive care units and more patients in the surgical/burn/trauma ICUs received PTZ/VAN. However, this study assessed AKI with three to five days of combination antibiotic therapy. The incidence of AKI in this study also increased as the vancomycin trough increased.

The study by Schreier et al reviewed here included a large cohort of critically ill patients from mixed ICU settings, used validated risk scores, and applied a rigorous multivariable model to determine risk. More than one-third of patients exposed to β-lactam/vancomycin developed AKI with a short course of therapy, with most of those developing stage 1 AKI. Additionally, when therapy was de-escalated rapidly, the risk of AKI was identical regardless of type of β-lactam/vancomycin combination chosen. It appears that if therapy lasts for less than three days, the risk of AKI is not different for the most commonly used β-lactam/vancomycin combinations regardless of the duration used inside the 72-hour "safe window." This finding points to the importance of obtaining relevant cultures early to facilitate early antibiotic de-escalation, within 72 hours or sooner. However, practitioners still need to be aware of the higher risk of AKI with PTZ/VAN combinations in the critically ill when used for more than three days, especially in surgical ICU patients. In scenarios necessitating prolonged empiric therapy for MDR organisms, combination therapy other than PTZ/VAN may be appropriate. ■

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Updates

By Carol A. Kemper, MD, FACP

Think You Don't Smell?

SOURCE: Fleming A. 'I don't smell!' Meet the people who have stopped washing. *The Guardian* Aug. 5, 2019.

The eco-revolution has spawned some interesting theories and crazy ideas. Not only do we have the paleo diet, but now we have paleo bathing — or, rather, non-bathing. Concerns have been raised that soaps are harmful to the skin, its natural odors, and its natural microbiome, leaving skin open to diseases such as acne and eczema and even bacterial super-infection. Indeed, certain soaps — and the overuse of hot water — can lead to dry skin and alter its pH. Not only are a growing number of people forgoing deodorants and soaps, some have gone from washing once a day to once a week or have stopped bathing altogether. Several companies are answering the call for "natural" skin care products intended to restore the normal skin oils and bacteria, including a burgeoning probiotic skin care industry. One French company uses heat deactivated lactobacillus in a lotion, while another United States-based company suspends microorganisms in a gel product.

[Although showering with hot water and harsh soap daily may not be optimal, studies have found that regular bathing with good soap and water reduces the risk of infection in individuals colonized with *Staphylococcus aureus*.]

After watching horses rolling in the dirt, one inventor harvested dirt samples from a local farm, attempted to analyze their function, and concluded that certain strains of bacteria that convert ammonia to nitrogen are necessary for maintaining a pleasant body odor. He created a "Motherdirt" mist spray containing a designated strain of ammonia-oxidizing bacteria to restore natural body odor. Now there are even "pre-biotics," which are intended to nurture the skin's existing microbes.

What is interesting is that many of these non-bathers claim they don't smell. However, our brains literally filter out our own body's odors and its byproducts. That is why the bathroom always smells worse after someone else uses it. Of course, these non-bathers have an odor; they just don't smell it themselves!

It is true that many mammals and birds survive without a hot shower and instead take "dust baths," the purpose of which has been debated for years. Studies suggest these may be one way to thermoregulate or rid the body of ectoparasites by literally knocking them off or smothering them with dust. Birds may use dust or dirt baths to remove excess oils from feathers so that they are fluffier and provide better insulation. But after watching my chickens roll around in the dirt, I can testify that they are not any cleaner, and they most certainly smell.

Although showering with hot water and harsh soap daily may not be optimal, studies have found that regular bathing with good soap and water reduces the risk of infection in individuals colonized with *Staphylococcus aureus*. I routinely advise daily baths with a good lye-based soap, a clean washcloth,

and lots of sudsing, especially to those areas where bacteria accumulate (axilla, perineum, groin, gluteal crease). With simple hygienic measures and freshly laundered clothing, many patients with methicillin-susceptible *S. aureus* or methicillin-resistant *S. aureus* folliculitis or boils improve. Besides, showers are one of the clear pleasures of the modern world. As the fictional time-traveling Claire Fraser of the "Outlander" series says, in choosing between the attractions of her 23-year-old husband in the 18th century and the benefits of living in the 20th century, hot showers almost won. ■

One-Fifth of Adults Have a Food Allergy

SOURCE: Gupta RS, Warren CM, Smith BM, et al. Prevalence and severity of food allergies among US adults. *JAMA Netw Open* 2019;2:e185630.

Are 19% of United States adults really allergic to a food? This survey, conducted by the non-partisan and objective research organization NORC at the University of Chicago from 2015-2016, is an extension of a national survey of food allergies conducted in children from 2009-2010. The primary outcome measure was the prevalence and severity of a convincing food allergy, based on the presence of at least one symptom on a stringent symptom list in adults in the United States. Food intolerance or symptoms not included in the expert panel's list of stringent symptoms were excluded. The survey was completed by 40,443 adults, with a mean age of 46.6 years.

Remarkably, 19% of adults reported at least one convincing or non-convincing food allergy. Among adults with a convincing food allergy, nearly half (48%) reported developing at least one food allergy in adulthood, whereas the other half developed their allergy before 18 years of age. Slightly more than half (51%) reported "severe" food allergies, and 45% reported allergies to multiple foods. One-third reported at least one food allergy-related emergency department visit in their lifetime. Roughly half were told by a physician that they had a food allergy, and one-fourth had a prescription for epinephrine.

[Much remains to be learned about the frequency and consequences of food allergies in adults, which are more common than previously believed.]

Women were nearly twice as likely as men to have current food allergies, and twice as likely to have developed a food allergy as an adult. The most common allergies were to shellfish (2.8%), milk (1.9%), peanuts (1.8%), tree nuts (1.2%), and fin fish (0.9%). The prevalence of food allergies did not appear to differ significantly between ethnicities, regions of residence in the United States, or household income.

Interestingly, earlier data suggested that approximately 10.8% of adults would report food allergy. This would correspond to approximately 26 million adults. Yet, this survey suggests that nearly twice as many people believe they have a food allergy to at least one food, and one-third of them have visited an emergency department for an allergic reaction to food. That's a lot of emergency department visits.

Much remains to be learned about the frequency and consequences of food allergies in adults, which are more common than previously believed. Or at least a lot of people think they have a problem. The obvious question is whether all these people have true allergies, or just think they do — or, worse, were convinced by a physician that their symptoms are the result of a food allergy and they are unnecessarily restricting their diet. ■

ABIM CME MOC ACCREDITED

CME INSTRUCTIONS

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CME QUESTIONS

1. Which of the following is true regarding urinary tract infection with bacteremia in a child younger than 2 months of age?

a. The clinician is obliged to provide parenteral antibiotics for at least 14 days.

b. It is often associated with recurrent infection within the month after initial treatment.

c. It responds nicely to treatment whether the initial antibiotic treatment is for more or less than seven days.

d. It is rare.

2. Which of the following is true in otherwise healthy, well-appearing, young, febrile infants who have pyuria?

a. Antibiotic treatment for a urinary tract infection is reasonable, even without concurrent testing to rule out meningitis.

b. Spinal fluid analysis is essential to rule out meningitis, since antibiotic doses for meningitis are different than doses for urinary tract infections.

c. There is good agreement among pediatric practitioners about supplemental diagnostic testing.

d. It would be malpractice not to perform cerebrospinal fluid testing.

3. Which of the following is correct regarding the retrospective study of short-course administration (> 24 to < 72 hours) of combination vancomycin and antipseudomonal beta-lactam therapy in critical care patients?

a. Acute kidney injury (AKI) was observed in approximately one-third of patients.

b. Vancomycin with piperacillin-tazobactam administration was associated with a significantly higher incidence of stage 2 or 3 AKI than other combinations.

c. Vancomycin with meropenem administration was associated with a significantly higher incidence of stage 2 or 3 AKI than other combinations.

d. Vancomycin with cefepime administration was associated with a significantly higher incidence of stage 2 or 3 AKI than other combinations.

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.