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Infectious Disease [ALERT]

Incisive Commentary and Clinical Abstracts on Current Issues in Infectious Diseases

ABSTRACT & COMMENTARY

Think Twice About That Fluoroquinolone Prescription

By Stan Deresinski, MD, FACP, FIDSA

Dr. Deresinski is Clinical Professor of Medicine, Stanford University.

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

SYNOPSIS: The FDA warns that serious side effects associated with fluoroquinolone antibacterial drugs generally outweigh the benefits for patients with sinusitis, bronchitis, and uncomplicated urinary tract infections who have other treatment options.

SOURCE: FDA Drug Safety Communication. Available at: www.fda.gov/downloads/Drugs/DrugSafety/UCM500591.pdf. Accessed May 16, 2016.

On May 12, 2016, the FDA issued a drug safety communication warning about potentially disabling side effects associated with the use of fluoroquinolone antibiotics, advising that their use be restricted. In particular, they advised that those side effects "… generally outweigh the benefits for patients with sinusitis, bronchitis, and uncomplicated urinary tract infections who have other treatment options" and that fluoroquinolones should not be used for those infections unless there are no alternative treatment options.

These concerns regarding the safety of this class of drugs (*see Table 1*) are not new. The FDA initially updated the drug labels to include a warning of cardiac arrhythmias in 1999, with further updates in 2001, 2004, and 2007. A warning regarding tendon rupture first appeared in 1996 and was updated in 2004 and 2007, while a warning about peripheral neuropathy was added initially in 2004 and updated in 2013. But these warnings were deemed insufficient by an advisory panel that met in November 2015 and decided that stronger statements were warranted.[1] Importantly, they further concluded that the balance of benefits and

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This CME activity is intended for the infectious disease specialist. It is in effect for 36 months from the date of the publication.

Table 1. Fluoroquinolone Safety Labeling*

Boxed Warning
- Tendinopathy and tendon rupture (increased risks: age > 60 years, concomitant corticosteroids, solid organ transplant)
- Exacerbation of myasthenia gravis

Warnings and Precautions Section
- Hypersensitivity reactions
- Hepatotoxicity
- Central nervous system effects
(altered mental status, seizures, tremors, psychosis, pseudotumor cerebri)
- Peripheral neuropathy (potentially irreversible)
- QT prolongation, torsades de pointes
- Blood glucose disturbance
- Photosensitivity/phototoxicity

* Recent reports (not included in the labeling) have also suggested increased risks of retinal detachment and aortic aneurysm rupture.

risks of use of systemically administered fluoroquinolones do not support their current labeled indications for use in the treatment of acute bacterial sinusitis, acute exacerbations of chronic bronchitis, or uncomplicated urinary tract infections. This was not an equivocal recommendation — the votes for these conclusions were overwhelming.

Infectious Diseases Society of America guidelines recommend fluoroquinolones as an alternative to first-line antibiotics (nitrofurantoin, fosfomycin, trimethoprim-sulfamethoxazole) for the treatment of uncomplicated urinary tract infections. Antibiotic therapy is not recommended in acute bronchitis (which is almost always caused by viruses), but it does provide benefit for patients with moderate-to-severe (not mild) acute bacterial exacerbations of chronic bronchitis. But in the case of these infections, fluoroquinolones are considered only as an alternative to first–line therapy. Like acute bronchitis, acute sinusitis is overwhelmingly of viral, not bacterial, etiology. As a consequence, antibiotics are only recommended for selected patients with very severe disease, with "double-sickening" (improvement followed by worsening suggestive of bacterial superinfection), or non-improving symptoms for at least 10 days.

Thus, even prior to the FDA warning, fluoroquinolones (and other antibiotics) had no role in the management of patients with acute bronchitis, or in the overwhelming majority of patients with acute sinusitis, and are not a first-line choice in patients with moderate-to-severe acute exacerbations of chronic bronchitis. They are also not among the first-line choices for treatment of uncomplicated urinary tract infection. Despite this, in 2014 in the United States, at least 22.2 million individuals (32.8 million total prescriptions) received a prescription for a fluoroquinolone. There is obviously a disconnect between both the published data and authoritative recommendations and actual clinical practice. Perhaps this warning from the FDA will give us a reminder to remember the first rule of medical practice — *primum non nocere* — and force us to reconsider our (and our colleagues') uses of fluoroquinolones. ■

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1. 2015 Meeting Materials, Antimicrobial Drugs Advisory Committee (formerly known as the Anti-Infective Drugs Advisory Committee). November 5, 2015 Meeting of the Antimicrobial Drugs Advisory Committee. www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/ucm424449.htm.

ABSTRACT & COMMENTARY

HLH Gene Mutations and Fatal Influenza

By Dean L. Winslow, MD, FACP, FIDSA

Dr. Winslow is professor of medicine, Division of General Medical Disciplines, Division of Infectious Diseases and Geographic Medicine, Stanford University School of Medicine.

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

SYNOPSIS: Sixteen patients with fatal influenza who underwent autopsy were studied. Thirteen patients (81%) had histopathologic evidence of hemophagocytosis. Five patients (36%) carried one of three heterozygous *LYST* or *PRF1* mutations associated with hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS).

SOURCE: Schulert GS, Zhang M, Fall N, et al. Whole-exome sequencing reveals mutations in genes linked to hemophagocytic lymphohistiocytosis and macrophage activation syndrome in fatal cases of H1N1 influenza. *J Infect Dis.* 2016;213:1180-1188.

All 16 patients with fatal influenza A (H1N1) infection at the University of Michigan Hospitals from 2009-2014 who underwent post-mortem examination were evaluated for the presence of hemophagocytic lymphohistiocytosis (HLH). All of these patients met at least two criteria for clinical diagnosis of HLH and 14 met criteria for macrophage activation syndrome (MAS). Thirteen (81%) had histopathologic evidence of hemophagocytosis at autopsy and by record review; all of these patients had clinical and laboratory features of HLH using modified HLH-2004 and macrophage activation syndrome criteria. Fourteen specimens underwent whole-exome sequencing. Known familial HLH gene mutations were identified in *PRF1* (two patients) and *LYST* (four patients). In addition, other HLH variant genes of interest were identified in five patients. The patient-derived *PRF1* mutant cDNA was generated from wild type *PRF1* cDNA by site-directed mutagenesis and cloned into a lentiviral expression vector, then transfected into HEK293T NK cells. The NK cells expressing lentiviral-transduced mutant *PRF1* demonstrated reduced cytotoxicity against K562 erythroleukemia target cells.

■ COMMENTARY

HLH remains a partially understood disease, but interesting insights into its pathogenesis have been gleaned over the past decade. Familial HLH (fHLH) is a rare autosomal recessive disorder manifested by severe multisystem inflammation, which is generally fatal without hematopoietic stem cell transplantation. fHLH has been shown to be caused by mutations affecting the cytolytic pathways of NK and CD8+ T-cells, especially the genes encoding perforin and proteins essential for the trafficking and fusion of perforin-containing granules. Reactive HLH (rHLH) tends to occur in older children and adults in response to a variety of infections. Its pathogenesis is less well understood than is fHLH, but recent reports show that many of the same (or closely related) gene variants associated with fHLH are present in cases of rHLH.

It has been known for many years that patients with severe, life-threatening H1N1 influenza often manifest features of HLH/MAS, including hyperinflammation, pancytopenia, coagulopathy, and liver dysfunction. The demonstration in this study that the majority of patients with fatal influenza who underwent autopsy were found to have histopathologic evidence of hemophagocytosis sheds light on the pathogenesis of severe influenza. The additional demonstration of gene variants known to be associated with familial HLH is fascinating and certainly points to the need for further study of the pathogenesis of severe influenza with an eye toward eventual exploration of potential interventions to inhibit the overwhelming inflammatory response seen in severe influenza infection. ■

ABSTRACT & COMMENTARY

The Seasonality of Childhood Respiratory Infections

By Philip R. Fischer, MD, DTM&H

Dr. Fischer is 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: Human metapneumovirus infection is increasingly recognized in children. Epidemiologic review suggests that it becomes common each winter after the onset of the respiratory syncytial virus "season" and then continues to cause frequent illness until the spring.

SOURCE: Haynes AK, Fowlkes AL, Schneider E, et al. Human metapneumovirus circulation in the United States, 2008-2014. *Pediatrics* 2016;137:e2015-2927.

Human metapneumovirus was first identified 15 years ago and is now known to cause both upper and lower respiratory tract infection. Young children in particular are susceptible to bronchiolitis and pneumonia due to this virus, and there are approximately 20,000 U.S. children hospitalized each year because of this infection. Clinically, pediatric metapneumovirus infection is similar to both respiratory syncytial virus and influenza virus infections. It had been thought that North American infections with metapneumovirus usually occurred in the winter and spring, but Haynes and colleagues conducted a nationwide epidemiologic review to more specifically understand the seasonality of metapneumovirus in relation to the seasonal patterns of influenza and respiratory syncytial virus.

Hundreds of clinical and public health laboratories contribute tens of thousands of samples to the National Respiratory and Enteric Virus Surveillance System each year. Samples from the most active laboratories were included in this study. Antigen detection and polymerase chain reaction methods were used. The viral "season" was defined as beginning and ending when the percentage of samples positive for a specific virus rose above 3% and then declined below 3%.

The study included 945,836 metapneumovirus tests with 3.6% being positive, 1.8 million respiratory syncytial virus tests with 15.3% positive, and 2.2 million influenza tests with 18.2% positive from July 2008 through June 2014 from 60 laboratories in 30 states. While there were some variations in times of viral activity from year to year, the median active seasons and peak months are noted in Table 1.

Typically, viral activity increases annually first for respiratory syncytial virus, then for influenza, and finally for human metapneumovirus. However, there was some activity of these viruses throughout the years of testing. Interestingly, the human metapneumovirus season shifted forward and back by about one month each year so that alternate years had relatively earlier and later seasons.

■ COMMENTARY

It is interesting to know when various viruses are "in season." For respiratory syncytial virus and influenza, knowledge of seasons prompts the timing of vaccination programs. Since there is currently no specific vaccine or curative treatment for metapneumovirus, there is not yet a specific therapeutic change to make based on this understanding of seasonality.

IS TESTING FOR HUMAN METAPNEUMOVIRUS CLINICALLY VALUABLE?

Since there is no specific therapeutic intervention for human metapneumovirus infection, does testing have clinical value (beyond the epidemiologic value of understanding seasons)? This question is especially important since diagnostic respiratory infection "panels" are increasingly available, whereby multiple infectious agents can be sought with a single test panel, for a significant cost.

First, one must be cognizant of the problem of assuming causality when a specific agent is identified in a sick child. A case-control study reported from Sweden last year included preschool-aged children with community-acquired pneumonia and compared them to healthy control children.[1] Human metapneumovirus, respiratory syncytial virus, adenovirus, and influenza virus were found significantly more commonly in sick than in well children. Bocavirus and coronavirus were found more commonly in well than in sick children.

Table 1. Median Active Seasons and Peak Months

Virus	Months in Season	Month of Peak Positivity
Human metapneumovirus	January – May	March
Respiratory syncytial virus	November – March	January
Influenza	December – May	January

Enterovirus, parainfluenza, and rhinovirus were found similarly in sick and well children (with rhinovirus found in about one-fourth of all children whether they were sick or not). Simply finding a virus in a sick child does not prove causality, but finding metapneumovirus, influenza, or respiratory syncytial virus is suggestive that it is etiologically related to the illness.[1,2]

Second, it has been postulated that identification of a potentially causative virus in a sick child might reduce testing and treatment of possible bacterial infection. In a Cochrane review of emergency department-based studies, identification of a presumptive viral cause for a child's febrile respiratory illness reduced the number of chest X-rays obtained but did not alter antibiotic use.[3] However, positive respiratory panel results for viral agents did reduce antibiotic use and length of inpatient stay in hospitalized children in a different study.[4]

WHAT DETERMINES THE SEASONALITY OF VIRAL RESPIRATORY INFECTIONS?

Seasonality of viral respiratory infections occurs in other parts of the world as well, but the seasons are a bit different. In Hong Kong, influenza A peaks in late January to mid-March but then has a smaller wave of activity from May to early September. There, respiratory syncytial virus has broader consistent activity from late February to mid-September. Interestingly, environmental temperature correlated with the times of influenza and respiratory syncytial virus infection but did not correlate with adenovirus activity. Influenza A was more prevalent during times of low rainfall, but respiratory syncytial virus was seen less during those drier times of the year.[5]

Controlled animal studies support the link between temperature and humidity, on one hand, and respiratory viral infection on the other.[6] Transmission of influenza between guinea pigs depends both on temperature and humidity. Transmission is more efficient in low temperatures (such as 5°C) and essentially blocked at higher temperatures (30°C). Dry conditions were also more favorable toward the spread of influenza than either moderate or high humidity conditions.[6] This is consistent with indoor (low humidity) cold weather (low temperature) spread of influenza in humans during winter time. The reasons for this are likely multifactorial, depending both on the virus and the potential hosts. Influenza virus is stable in low humidity and is potentially inactivated at higher temperatures.[6] On the host side, cooling of the nasal mucosa inhibits mucociliary clearance.[6] In addition, transmission of virus between people depends on droplets; in low humidity, water evaporates from respiratory droplets, making the droplets smaller and better able to stay suspended in the air for transmission over longer distances.[6]

The humidity of school classrooms varies between schools and throughout days and seasons.[7] Charlie Huskins and his colleagues have shown that using classroom humidifiers for four hours can increase humidity enough to potentially decrease viral survival by 30%.[7] Perhaps one way to limit influenza transmission would be to humidify indoor spaces during winter time.

Other environmental factors also can facilitate the spread of respiratory viruses. In China, there is a strong positive relationship between high levels of air pollution and the incidence of influenza.[8] This relationship held even when the analysis was controlled for humidity and temperature.[8]

Thus, respiratory virus transmission follows seasonal patterns related to temperature, humidity, and air pollution. Some of these factors are potentially modifiable in specific areas where children are at risk. ■

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ABSTRACT & COMMENTARY

Oral Rehydration for Children with Mild Gastroenteritis

By Hal B. Jenson, MD, FAAP

Dr. Jenson is Professor of Pediatric and Adolescent Medicine, and Dean, Western Michigan University Homer Stryker M.D. School of Medicine, Kalamazoo, MI.

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

SYNOPSIS: In a randomized study of children 6 to 60 months of age with acute gastroenteritis accompanied by mild vomiting and/or diarrhea with mild or no dehydration, initial oral rehydration with half-strength apple juice/preferred fluids resulted in fewer treatment failures than with electrolyte maintenance solution. In high-income countries, dilute apple juice/preferred fluids may be an acceptable alternative to commercial electrolyte maintenance solutions for childhood mild gastroenteritis with minimal dehydration.

SOURCE: Freedman SB, Willan AR, Boutis K, et al. Effect of dilute apple juice and preferred fluids vs. electrolyte maintenance solution on treatment failure among children with mild gastroenteritis: A randomized clinical trial. *JAMA* 2016;315:1966-1974.

A randomized, single-blind, noninferiority trial was conducted among 647 children 6 to 60 months of age with gastroenteritis with mild or no signs of dehydration between the months of October and April during the years 2010 to 2015 in Toronto, Canada. Children with less than 96 hours of symptoms with three or more episodes of vomiting or diarrhea within the preceding 24 hours were randomly assigned to receive half-strength apple juice/preferred fluids or color-matched electrolyte maintenance solution (pediatric electrolyte). Parents were given 2 L of fluid for use in the emergency department and at home, and instructed to give 5 mL aliquots every two to five minutes, replacing 2 mL/kg per vomiting episode and 10 mL/kg per diarrheal episode. Children who vomited received oral ondansetron.

Treatment failure was defined as hospitalization, intravenous rehydration, unscheduled physician visits for the same illness, protracted symptoms for more than seven days, physician request to change therapy, or 3% or greater weight loss at follow-up.

Among 647 randomized children (mean age, 28.3 [SD, 15.9] months) with 331 boys, and 441 without clinical signs of dehydration, 323 were randomized to apple juice and 324 to electrolyte maintenance solution. Baseline characteristics were similar. At least one follow-up was obtained in 99.5% of participants.

In the intent-to-treat analysis, the failure rate was 16.7% (54/323, 95% CI, 12.8-21.2%) for apple juice, and 25% (81/324, 95% CI, 20.4-30.1%) for electrolyte maintenance solution. This was statistically significant, with $P < 0.001$ for inferiority and $P = 0.006$ for superiority. Intravenous rehydration at the index visit was required less frequently for children receiving apple juice compared to electrolyte maintenance solution (0.9% [3/323] vs. 6.8% [22/324]; difference -5.9%; 95% CI, -10.5% to -2.0%; $P < 0.001$). Post hoc analysis revealed a lower overall seven-day intravenous rehydration rate among children receiving apple juice compared with electrolyte maintenance solution (2.5% [8/323] vs. 9.0% [29/324]; difference, -6.5%; 99% CI, -11.6 to -1.8%). Rates of diarrhea, vomiting, and hospitalizations were not significantly different between the groups. No episodes of significant hyponatremia were found.

■ COMMENTARY

Acute gastroenteritis remains the second cause of childhood deaths worldwide. Improved fluid management has resulted in lower mortality rates globally, and universal vaccination with rotavirus vaccines in developed countries has significantly mitigated the impact of rotavirus disease. During an episode of acute gastroenteritis, ondansetron reduces the incidence of vomiting and is well established as an adjunct for managing acute gastroenteritis in developed countries.

Mild dehydration in children is difficult to detect clinically. The best parameter to gauge dehydration is comparing accurate weights immediately before the illness and at presentation, though this data is not often available. Loss of 3-5% of body weight

is generally required before showing even mild signs of dehydration, and physical findings of dehydration may be subtle or even normal with 7-10% dehydration. The findings of the current study apply to children with no or minimal dehydration, which applies to the majority of children with acute gastroenteritis.

Oral rehydration is the mainstay of fluid management for acute gastroenteritis except for those children with signs of shock or who are unable to tolerate oral fluids because of severe vomiting. Low-osmolality oral rehydration solutions are preferred and the global standard of care. Other fluids, such as decarbonated soda beverages, fruit juices, and tea, are not considered suitable for rehydration primarily because of their high osmolalities and low sodium concentrations. There has been concern about using these solutions because of possible risk of osmotic diarrhea, and water intoxication with hyponatremia.

The results of this study challenge this dogma for managing children with acute gastroenteritis (less than 96 hours of symptoms) with minimal (< 5%) or no dehydration. Another study from Brazil also challenges the concern about the clinical significance of the high osmolality of alternative solutions, showing minimal impact among children even with severe diarrhea.

In high-income countries, the use of half-strength apple juice and fluids preferred by the child may be an appropriate alternative to electrolyte maintenance solution for children with mild acute gastroenteritis and no or minimal physical signs of dehydration. ■

ABSTRACT & COMMENTARY

Does Finding the Portal of Entry of Bacteria in Infective Endocarditis Matter?

By Michael H. Crawford, MD

Dr. Crawford is Professor of Medicine, Chief of Clinical Cardiology, University of California, San Francisco.

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

SYNOPSIS: A comprehensive, systematic search for the portal of bacterial entry in infective endocarditis is frequently successful and affords an opportunity to prevent recurrent episodes.

SOURCES: Delahaye F, et al. Systematic search for present and potential portals of entry for infective endocarditis. *J Am Coll Cardiol* 2016;67:151-158.

Chu VH. When the cat's out of the bag: Searching for portals of entry in infective endocarditis. *J Am Coll Cardiol* 2016;67:159-161.

It would seem that the portal of entry (POE) of the microorganisms responsible for infective endocarditis (IE) is important to prevent further episodes, which occur in up to 30% of patients with IE. However, little data on this topic exist. Thus, investigators from Lyon, France, prospectively and systematically sought the POE in all cases of IE admitted between 2005 and 2011. A dentist, an ENT physician, and a urologist examined all patients. A gynecologist also examined all female patients. If skin lesions were present, a dermatologist saw them. Patients also underwent dental, cerebral, and thoracic-abdominal-pelvic X-rays. If the organism identified originated in the gastrointestinal (GI) tract, if the patient was > 50 years of age, or if there was a family history of colon polyposis, patients received a colonoscopy. For each case, the most probable POE was inferred from the results of these tests and the natural habitat of the identified causative microorganism. Researchers performed treatment of the POE where feasible. From 444 IE admissions, 82 were excluded because they died in hospital and 44 were excluded for incomplete data, leaving 318 patients with 320 episodes of IE. In 74% of patients, researchers identified a POE; of these, 40% were cutaneous, 29% oral or dental, and 23% were GI. The majority of cutaneous sources were related to healthcare or IV drug use. Dental infections were the source for the majority with oral/dental POEs, rather than dental procedures (59% vs. 12%). Half of those with GI POEs had colonic polyps. The authors concluded that the search for a POE in patients with IE is frequently successful, and they advise a systematic oral examination in all and colonoscopy in selected patients with IE.

■ COMMENTARY

Prevention of IE has revolved around antibiotic

prophylaxis for procedures likely to result in significant bacteremia in individuals at high risk of IE. One of those high-risk features is previous IE. So, efforts to identify the likely POE and treat or eliminate it would make sense. However, not only is there little literature on this topic, but physicians pay scant attention to it in patients with IE. This study is remarkable in its comprehensive approach to finding the POE. Researchers were able to identify a likely POE in about three-quarters of their patients. In about one-third, researchers discovered additional potential POEs for new episodes of IE. Although not assessed in this study, it is hard to argue that treating these POEs and potential POEs would not have a beneficial effect.

Based on the results of this study, a more streamlined and cost-effective approach to finding the POE emerged. Routine ENT or GU evaluations were low yield and should be reserved for those with evidence of infections in these areas. On the other hand, a comprehensive oral exam was high yield (53%). It constituted a dental exam and panoramic X-rays of the teeth. Of the oral POEs, 59% were tooth infections, some only detected by X-ray, and 28% were periodontal. Only 12% were related to dental procedures. Colonoscopy was also high yield (40%) in a high-risk subgroup, age > 50 years, or a family history of colonic polyposis. In addition, a dermatologist examined those with suspicious skin lesions. Healthcare-associated skin issues were identified in 41%, and 34% had community-acquired lesions. The former included vascular access (44%), EP devices (28%), and operative wounds (28%). The latter included IV drug use (22%) and insect bites or cat scratches (3%). The rest had ulcers and other wounds.

The study's major weakness is that the role of organism identification (performed in all but nine cases) in determining the POE is not spelled out clearly. Not all POEs were cultured and those that were did not undergo genetic analysis to see if they were the same organism identified in the blood cultures. However, the likely POE correlated well with the known body habitat of the organisms identified by blood culture. Also, in 25% with no POE discovered, the distribution of the organisms was similar to that found in those with a POE identified. In addition, the authors did not discuss the possibility of multiple POEs.

In summary, patients with high-risk cardiac conditions for IE, such as prosthetic valves or other material, EP devices, and certain types of congenital heart disease, not only need antibiotic prophylaxis for IE, but should have any infections treated expeditiously. Those with IE should have reasonable efforts to find the POE and treat it if feasible. The type of exams performed could be guided by the organisms found: a careful skin exam in those with Staph. species, an oral exam and dental X-rays in those with oral Strep. species, and colonoscopy in those with GI organisms detected. ■

Healthcare Workers and Tuberculosis Prevention

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

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

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

SOURCE: Evans TG, Bekker L-G, eds. Healthcare workers and tuberculosis prevention. *Clin Infect Dis* 2016;62(suppl3):S229-S280.

CLINICAL PROBLEM

A 22-year-old woman native of South Carolina presented to an emergency department (ED) with right-sided chest pain. She was afebrile and not coughing. As a toddler, she was exposed to her aunt who had cavitary tuberculosis. The daughter of that aunt contracted tuberculosis. Both the aunt and child were treated with anti-tuberculosis therapy. As a child with contact, the patient was given anti-tuberculosis prophylaxis for six to eight months, as she remembered. She said she was adherent to the prophylaxis. She was unable to produce any expectorated sputum.

On exam, her vital signs were normal and there were minimal findings. The right side of the chest was tender to palpation. The chest film and chest CT showed minimal pleural reaction of the right lung, but a large left upper lobe cavitation. Initial

laboratory findings were unremarkable.

The emergency physicians had several questions: Are there provisions for handling the patient before hospital admission? Have emergency personnel had a significant exposure? How can personnel be tested for infection? Should the patient be treated immediately?

■ COMMENTARY

Along with HIV, tuberculosis (TB) remains the leading cause of death worldwide. Even though these deaths occur in 22 so-called high-burden countries, TB remains a problem in the United States. Multidrug-resistant TB now accounts for 3.3% of new cases but 20% of repeat cases. Prophylaxis, when used, remains an effective cornerstone of prevention. Healthcare workers (HCWs) in high-burden countries in particular remain at high risk of TB. Every 21 seconds, a person dies of TB, including some healthcare professionals.

The ED physicians noted above have very important and meaningful questions. The May 15, 2016, supplement to *Clinical Infectious Diseases* is devoted to a single topic: Healthcare Workers and Tuberculosis Prevention. There are seven provocative original articles, primarily from South Africa, but with information and data applicable worldwide.

Central to these articles is the theme of protecting our front-line HCWs. Very few of the high-burden countries have TB infection control reporting. We are very lucky in the United States to have dealt with prevention of TB in HCWs, but we can always do more, as evidenced by the questions that arose in the case described. There are four defenses put forward by Verkuijl and Middelkoop in the first article. Four lines of defense from exposure to tuberculosis in healthcare workers are managerial, administrative, environmental, and personal. At all times the fears of HCWs must be taken into account, in some cases to insure that information on drug resistance comes quickly to infection control in the event that infection would occur in an HCW.

Because of rapid air travel and fluid national borders, citizens of high-burden countries quickly can become residents of developed countries, presenting problems of TB contagion to first-world healthcare systems. For that reason, the strategies throughout this symposium based on high-burden countries resonate with implications for more developed nations.

The article by Tudor et al finds that the major occupational risk for TB for HCWs in KwaZulu-Natal is HIV, a finding that can perhaps be extended to our HCWs who may be immunosuppressed. In the last article by von Delft et al, HCWs and students in Cape Town have the impression, right within their resource-poor setting, that they are not susceptible to TB, even though there is a high degree of occupational TB exposure. Clearly there is a need for funding at a much higher level to protect HCWs from acquisition of TB. The articles in this symposium highlight that immense need.

As for our patient described in the case, it turned out that the initial acid fast smears were positive, suggesting TB was actually the cause of the cavitary disease. The patient was placed into a negative-pressure room present in the ED. The patient was not coughing to any extent, so the exposure to ED personnel may be reduced, but there was some exposure concern before the patient was placed into the negative-pressure room. Standard tuberculin testing should be performed after HCWs have had adequate time to make a delayed type skin response. Some hospitals would make testing for gamma-interferon release available (Quantiferon testing), but the ideal time for Quantiferon testing after an exposure has not yet been established. The patient was placed on an anti-tuberculosis regimen consisting of four agents the second day of admission. More rapid means of determining if *M. tuberculosis* is the pathogen are in development and would certainly add to the quality of care in the present case. ■

Infectious Disease [ALERT]

Updates

By Carol A. Kemper, MD, FACP

"A New Wave of World-wide Gastroenteritis?"

SOURCE: de Graaf M, van Beek J, Vennema H, et al. Emergence of a novel GII.17 norovirus — End of the GII.4 era? *Euro Surveill* 2015;20:21178.

The unexpected appearance in Japan of a previously relatively uncommon norovirus genotype, responsible for a series of gastroenteritis outbreaks at the end of 2014/winter 2015, has led to speculation that a new cycle of norovirus outbreaks is beginning.

Norovirus is likened to a "shape shifter" because of its frequent evolutionary antigenic changes,

taking advantage of gaps in human immunity to re-emerge in new cycles of infection every few decades. Of the 30 or so genotypes in circulation, only seven have been seen with any frequency, and one (GII.4) has been predominant since the 1990s, responsible for 70% to 80% of gastroenteritis illness around the globe. The antigenic changes of GII.4 virus have, however, gone beyond the usual changes seen in "drifted" virus, instead engaging in infra-genotypic recombinations in their open reading frames (all of which is accomplished asexually). As such, GII.4 Sydney replaced the GII.4 New Orleans strain as the dominant world-wide strain in 2012-2013. Over the past few years, norovirus outbreaks have gradually diminished as the global population developed immunity to the GII.4 viruses. Amazingly, all of this is tracked by the Noronet database, which monitors outbreaks of norovirus around the globe.

Enter GII.17. Like "C-beams glittering in the dark near the Tannhauser gate," everything is lost in time. GII.17 has been circulating at low levels for nearly four decades, resulting in sporadic outbreaks in Africa and South America. But during the past two to three years, GII.17 Kawasaki 2014 virus has emerged as the predominant strain associated with outbreaks in China, Korea, and Japan, and appears poised to cause a world-wide explosion — of diarrhea.

Current efforts at development of a norovirus vaccine have been aimed at the most common circulating genotypes. It remains to be seen whether vaccine–induced immunity will cross-react with GII.17. Current norovirus assays for detection of clinical infection will also need to be re-evaluated, to ensure they include this additional genotype.

Who Wants a Stoma if You Don't Need One?

SOURCE: Thornell A, Angenete E, Bisgaard T, et al. Laparoscopic lavage for perforated diverticulitis with purulent peritonitis: A randomized trial. *Ann Intern Med* 2016;164:137-145.

Perforated diverticulitis resulting in purulent or fecal peritonitis historically has been treated with surgical control of the offending bowel with urgent open bowel resection and formation of an ileostomy or colostomy (called a Hartmann procedure, which involves sigmoid resection and end colostomy). Occasionally, a few lucky patients were candidates for resection of the affected portion of bowel with an end-to-end anastomosis without creation of a stoma. Patients with perforated diverticulitis suffered through the morbidity of the open surgical resection, which, in the elderly, was not inconsiderable, and eventually many patients were faced with the choice of re-operation for "take-down" or reversal of the stoma. In lieu of this approach, it has been debated for years whether laparoscopic lavage might offer a less invasive, less morbid approach for certain patients.

These authors prospectively assessed outcomes in 83 patients randomly assigned to surgical control (Hartmann's procedure) vs. laparoscopic lavage or drainage. The primary endpoint was the percentage of patients requiring re-operation within 12 months. Interventional radiologic drainage and surgical stoma reversal were counted as re-operations. Secondary outcomes included duration of hospital stay, the number of re-admissions and procedures within a 12-month period, adverse events, and morbidity.

Patients with suspected purulent diverticulitis (not fecal peritonitis), as confirmed by evidence of free air and/or peritoneal fluid on radiographic studies, were randomly assigned by an evaluating surgeon as they presented for care. Only those individuals who were otherwise considered surgical candidates were enrolled in the study.

Of the 83 randomized patients, eight (9.6%) were found to have other reasons for their presentation, including four with colon cancer, three with small bowel perforations and/or ischemia, and one with gynecologic malignancy. One withdrew consent, and another patient ended up with an entirely different surgical procedure and was excluded. Of the remaining 73 patients, 38 underwent laparoscopic lavage and 35 surgical resection. Mean hospital stays were shorter for lavage patients compared with surgical patients (14 vs. 18 days, P = 0.047).

Interestingly, within 12 months, 25 (62.5%) patients in the surgical control group compared with 12 (28%) in the lavage group had one or more re-operations; 21 of those in the surgical group were for reversal of the stoma. Nearly one-third (29%) of the patients in the lavage group developed abscess, and two later required open surgical resection. In comparison, six (17%) in the surgical group developed abscess and one required re-operation. By 12 months, 14 (37%) patients in the lavage group developed abscess, and seven patients required re-admission for recurrent diverticulitis. In comparison, 21 patients in the surgical group required re-admission for stoma reversal. At the end of one year, seven patients in the lavage group had a stoma, compared to 28 patients in the surgical control group. Six patients in each group died.

As with most things, it's all about how you look at the data. Two earlier clinical trails examining this same question came down on the side favoring surgical resection — morbidity from sepsis was better controlled, and the number of re-operations — not including stoma reversal — were fewer. These authors included both interventional radiologic procedures and stoma reversal as "surgical procedures" — which greatly skews the data toward laparoscopic lavage as resulting in fewer adverse events, fewer hospital days, and fewer "re-operations."

Aside from these differences in how the data were assessed, the two approaches were fairly similar in their outcomes and mortality. Granted, no one desires a stoma, let alone a second surgical procedure for reversal. But the key here is disease control — many of these patients are critically ill with sepsis, on multiple antibiotics; more than one-third of the lavage patients developed abscess and/or required re-hospitalization for recurrent diverticulitis within 12 months. How many more will do so within their lifetime? Further, nearly 10% of the patients had an alternative diagnosis for the presentation, including 5% with malignancy — a diagnosis not made by lavage. If nothing else, surgical resection provides direct pathologic examination and removes the diseased organ. The accompanying editorial suggests that future research focus on identifying that subgroup of perforated diverticulitis patients most amenable to less invasive technologies.

A Side of Hep E with Your Pork Roast?

SOURCE: Guillois Y, Abravanel F, Miura T, et al. High proportion of asymptomatic infections in an outbreak of hepatitis E associated with a spit-roasted piglet, France, 2013. *Clin Infect Dis* 2016;62:351-357.

A cluster of three cases of acute hepatitis E (HEV) infection in October-November 2013 on a small coastal island off western France prompted an epidemiological investigation. The three individuals all lived in the same village, developed symptoms within a few weeks of one another, and all had attended the same wedding in September. HEV strains from the three individuals exhibited homology and belonged to the same subtype 3f (genotype HEV3).

A total of 111 persons attended the wedding party, which involved a buffet of five mixed salads; a piglet stuffed with dressing that included raw piglet liver and roasted on a spit; barbecued lamb; grilled potatoes; flageolets and carrots; eight different goat cheeses; and six desserts. A questionnaire was administered to 98 wedding participants, 52 of whom provided a blood sample for PCR and serological testing; 50 (96%) of these lived on the island. Anyone with symptoms of jaundice or who reported hospitalization provided a blood sample. Remarkably, 14 wedding guests (27%) were found to have evidence of past HEV infection and were excluded from the remaining analyses, and 17 acute HEV cases (32.7%) were identified. More than two-thirds of these infections (70%) were asymptomatic.

A retrospective cohort study found a significant correlation between acute HEV infection and ingestion of piglet stuffing. A visit to the piglet farm found that the drinking water used for the animals came from a surface pond below the stock manure pit. All nine samples of water and piglet manure were positive for HEV. In addition, HEV was detected in untreated sewage samples from two of the island's wastewater treatment facilities in December; samples from one of those facilities were still positive in late January 2014. All of the isolates were genotype 3f, and two of the HEV virus obtained from samples of liquid manure at the farm were 100% identical to the clinical specimens. Further analysis demonstrated that all of the isolates formed a distinct phylogenetic cluster.

The likely culprit for this outbreak was ingestion of inadequately cooked pork or pork liver, although the wedding foodstuffs were no longer available for direct testing and, given the frequency of previous HEV infection in the participants, any of the cooks could have theoretically been responsible. Based on serological data, HEV infection appears to be fairly common on this small French island — likely because of infection in their swine population. Nearly one-third of adults had been previously infected. An important observation from this study was the high frequency (70%) of subclinical infections, and the persistence of low-grade HEV infection in island wastewater samples several months later indicates sustained infection in the islanders. The authors noted that HEV is inactivated by cooking at 71°C (159.8°F) — not even above the temperature of boiling water — for at least 20 minutes. It's best to avoid eating undercooked meat when you travel. ■

CME INSTRUCTIONS

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CME QUESTIONS

1. The transmission of respiratory viruses:

a. follows seasonal patterns.

b. is more efficient in colder temperatures.

c. is more efficient at low humidity.

d. increases during days of heavy air pollution.

e. all of the above.

2. Which of the following is correct?

a. Fluoroquinolones are recommended as first-line antibiotics for acute sinusitis.

b. Fluoroquinolones are recommended as first-line antibiotics for acute bronchitis.

c. Fluoroquinolones are recommended as first-line antibiotics for acute exacerbations of chronic bronchitis.

d. None of the above are correct.

3. Which of the following is most correct with regard to labeled warnings about fluoroquinolone use?

a. Tendinopathy and tendon rupture

b. Peripheral neuropathy

c. Central nervous system effects

d. All of the above

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.