RELIAS
Formerly AHC Media

Vol. 37, Issue 4, January 2018
AHCMedia.com

Infectious Disease [ALERT]

Incisive Commentary and Clinical Abstracts on Current Issues in Infectious Diseases

ABSTRACT & COMMENTARY

Self-administered Weekly Therapy for Latent Tuberculosis Is Non-inferior to Directly Observed Therapy in the United States

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

Associate Professor of Internal Medicine, Northeast Ohio Medical University; Division of Infectious Diseases, Cleveland Clinic Akron General, Akron, OH

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

SYNOPSIS: A randomized clinical trial conducted in the United States and three other countries compared self-administered isoniazid and rifapentine with and without weekly reminders to directly observed therapy (DOT). Self-administered therapy without reminders was non-inferior to DOT in the United States; no other comparisons met non-inferiority criteria.

SOURCE: Belknap R, Holland D, Feng PJ, et al. Self-administered versus directly observed once-weekly isoniazid and rifapentine treatment of latent tuberculosis infection: A randomized trial. *Ann Intern Med* 2017;167:689-697.

Reducing the duration of treatment for latent tuberculosis has several potential benefits, including less risk for drug toxicities, better compliance, and lower costs. One regimen, isoniazid (INH) and rifapentine, is safe and effective when given once weekly for 12 doses, but is limited by the need for directly observed therapy (DOT). Belknap and colleagues compared the safety and completion rate of this regimen when given by DOT vs. self-administration.

The iAdhere study was a randomized clinical trial conducted at nine sites in the United States and one each in Spain, Hong Kong, and South Africa.

Financial Disclosure: *Infectious Disease Alert*'s Editor Stan Deresinski, MD, FACP, FIDSA, Peer Reviewer Patrick Joseph, MD, Updates Author Carol A. Kemper, MD, FACP, Peer Reviewer Kiran Gajurel, MD, Executive Editor Shelly Morrow Mark, Editor Jonathan Springston, and Editorial Group Manager Terrey L. Hatcher report no financial relationships to this field of study.

Infectious Disease [ALERT]

Infectious Disease Alert,
ISSN 0739-7348, is published monthly by
AHC Media, a Relias Learning company
111 Corning Road, Suite 250
Cary, NC 27518
AHCMedia.com

Periodicals Postage Paid at Cary, NC, and at additional mailing offices.

GST Registration Number: R128870672.
POSTMASTER: Send address changes to
***Infectious Disease Alert*, Relias Learning**
111 Corning Road, Suite 250
Cary, NC 27518-9238

SUBSCRIBER INFORMATION
(800) 688-2421
Customer.Service@AHCMedia.com
AHCMedia.com

Editorial Email:
mmark@reliaslearning.com

Subscription Prices
United States:
Print: 1 year with free *AMA PRA Category 1 Credits™*: $349
Add $19.99 for shipping & handling.
Online only: 1 year (Single user) with ***free*** *AMA PRA Category 1 Credits™*: $299

Back issues: Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.

Canada: Add 7% GST and $30 shipping.
Elsewhere: Add $30 shipping.

ACCREDITATION
Relias Learning is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

Relias Learning designates this enduring material for a maximum of ***3*** *AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 3 MOC Medical Knowledge points in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program. Participants will earn MOC points equivalent to the amount of CME credits claimed for the activity. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit.

Infectious Disease Alert may contain references to off-label or unapproved uses of drugs or devices. The use of these agents outside currently approved labeling is considered experimental, and participants should consult prescribing information for these products.

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

Patients were included if they were at least 18 years of age, males or nonpregnant females, and weighed at least 45 kg. Exclusion criteria included known or suspected active tuberculosis, known contact with someone who had drug-resistant tuberculosis, prior intolerance to either INH or rifapentine, prior treatment of active or latent tuberculosis for at least one week, baseline elevation of alanine aminotransferase more than five times the upper limit of normal, and antiretroviral therapy for HIV. The latter was because of potential drug-drug interactions with rifapentine.

Participants were assigned randomly to one of three groups: once-weekly INH and rifapentine by DOT; once-weekly therapy by self-administration; and once-weekly therapy along with weekly text message reminders. They were evaluated monthly for toxicity and therapy adherence. The primary endpoint was treatment completion, which was defined as receiving at least 11 doses within 16 weeks. Participants were followed for 28 days after receiving their last dose to assess for adverse events.

Of 2,177 patients screened, 1,002 were enrolled in the iAdhere study. The completion rate was 87.2% (95% confidence interval [CI], 83.1-90.5%) in the DOT group, 74.0% (95% CI, 68.9-78.6%) in the self-administered group, and 76.4% (95% CI, 71.3-80.8%) in the self-administered group with reminders. In the United States, the completion rate for DOT was 85.4% (95% CI, 80.4-89.4%), 77.9% (95% CI, 72.7-82.6%) in the self-administered group, and 76.7% (95% CI, 70.9-81.7%) in the self-administered group with reminders.

Factors associated with noncompletion by multivariate logistic regression included enrollment in South Africa compared to other locations, smoking, and female sex. There were 208 adverse events reported by 174 participants, with similar proportions among the three groups. Of these, 78 participants experienced drug-related adverse events, five of which were serious, and 45 participants discontinued treatment because of an adverse event. One death occurred among the participants (a suicide), but the death was determined to be unrelated to the study drugs.

■ COMMENTARY

Approximately 10% of individuals with latent tuberculosis progress to active tuberculosis during their lifetimes, which represents a major hurdle for controlling the global tuberculosis epidemic. The study by Belknap and colleagues offers new hope in the efforts to combat latent tuberculosis, with some important caveats. The researchers found similar completion rates for DOT and self-administered therapy from the clinical sites in the United States, but not from the site in South Africa. The high completion rate for INH and rifapentine was comparable to a recently published observational study.[1] Compared to participants from the other sites, those from South Africa were younger, more likely to be unemployed, more likely to abuse alcohol, and were mostly HIV-negative household contacts of someone with active tuberculosis. These factors likely contributed to the lower completion rate, which has potentially important implications for the role of self-administered therapy in global tuberculosis control.

If the results from South Africa are excluded, treatment completion of three months of INH and rifapentine by self-administration was higher in iAdhere than has been reported previously with nine months of INH, and is similar to four months of rifampin. Safety and tolerability are important concerns when treating latent tuberculosis since many of these individuals are healthy and do not take medications routinely, which may cause them to be especially intolerant of medicine-related side effects. Therefore, the results from iAdhere that the total, drug-related, and severe adverse events were comparable in the DOT and self-administered groups are encouraging. The finding from the United States that weekly reminders did not improve compliance and that this group actually showed lower compliance compared to the self-administered group that did not receive

reminders is surprising and should be evaluated further in future studies.

There were a few limitations to the study. Of the 12 study sites, only one was in a resource-limited setting (South Africa), so the results might not be generalizable to these regions. Also, the effectiveness of the weekly reminders is questionable because not all of the participants assigned to this group had access to text messages, and the investigators did not require confirmation that a message had been received.

The iAdhere study provides evidence that self-administered rifapentine and INH seems to be a viable option for treatment of latent tuberculosis in the United States. The authors of tuberculosis guidelines will need to consider the results of iAdhere carefully when deciding about future recommendations. ■

REFERENCE

1. Sandul AL, Nwana N, Holcombe JM, et al. High rate of treatment completion in program settings with 12-dose weekly isoniazid and rifapentine (3HP) for latent *Mycobacterium tuberculosis* infection. *Clin Infect Dis* 2017 May 30. doi: 10.1093/cid/cix505. [Epub ahead of print].

ABSTRACT & COMMENTARY

Spinal Epidural Abscess

By Stan Deresinski, MD, FACP, FIDSA

Clinical Professor of Medicine, Stanford University

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

SYNOPSIS: Non-operative management of spinal epidural abscess is safe and effective in selected patients.

SOURCE: Vakili M, Crum-Cianflone NF. Spinal epidural abscess: A series of 101 cases. *Am J Med* 2017;130:1458-1463.

Vakili and Crum-Cianflone reviewed the case records of 101 patients with spinal epidural abscess seen at a single hospital in San Diego between 2004 and 2014. The incidence during this time was 5.1 per 10,000 admissions. The most frequently encountered comorbid risk factor was diabetes mellitus, which was present in approximately one-fourth of cases. Additional risk factors included injection drug use in 16.8% and alcoholism in 14.9%, while 19.8% had undergone spinal surgery, 11.8% had suffered spinal trauma, and 6% had received a local injection; 26% had bacteremia.

Only eight (7.9%) of the patients presented with all three elements of the "classic triad" of spinal pain, fever, and neurologic deficit, with 47% presenting with only local pain and tenderness (stage 1). Radicular pain (stage 2) was present in 22%, while 11% had sensory, motor, bowel, and/or bladder dysfunction (stage 3). Paralysis (stage 4) was seen at presentation in 9% of cases.

Among the patients in whom a pathogen was identified, 59.4% of the infections were due to *Staphylococcus aureus*, 13.9% were caused by other Gram-positive coccal organisms, and 4.9% were due to aerobic Gram-negative bacilli. All patients received intravenous antibiotics, which were administered for a median duration of eight weeks. Of the entire cohort, 27% underwent a drainage procedure performed by an interventional radiologist (IR) and 47% underwent operative surgical drainage (three patients among this group subsequently required IR drainage). The remaining 27% underwent no invasive procedure and were treated with antibiotics alone.

At discharge, none of the 47 patients with a stage 1 presentation had evidence of paralysis, while this was present in 1/22 and 1/11 of those with stage 2 and 3 presentations, respectively. Six of nine patients with paralysis at presentation still demonstrated evidence of paralysis at discharge; seven of the nine had undergone surgery. No patient who underwent IR drainage alone and none who did not receive a drainage procedure were paralyzed at discharge. Seven patients, all with *Staphylococcus aureus* infection, died.

■ COMMENTARY

Over the last decade, there has been an evolution toward the non-operative management of selected patients with spinal epidural abscess. This retrospective cohort study validates this approach. In this study by Vakili and Crum-Cianflone, 27% did not undergo surgery and another 27% had only IR drainage — none of these patients had evidence of paralysis at hospital discharge.

Patients in this cohort received antibiotics for a median duration of eight weeks. Whether this is the appropriate duration of therapy is unknown and, in my opinion, is likely to be longer than necessary in most cases.

The key to a favorable outcome is early diagnosis and therapy. Unfortunately, the diagnosis often may be delayed. In a recent review, a national Veterans Administration study found evidence of diagnostic error in 66/119 (55.5%) patients with spinal epidural abscess.[1] These errors were associated with a significant prolongation in the median time to diagnosis, which was 12 days in those whose evaluation included an error and only four days in those without error. This is critical in many patients since it is generally agreed that surgical intervention must be performed within approximately 48 hours after the onset of paralysis to have a reasonable chance of its reversal. ■

REFERENCE

1. Bhise V, Meyer AND, Singh H, et al. Errors in diagnosis of spinal epidural abscesses in the era of electronic health records. *Am J Med* 2017;130:975-981.

ABSTRACT & COMMENTARY

Follow-up Blood Cultures in Gram-negative Bacteremia — Don't Order Them

By Dean L. Winslow, MD, FACP, FIDSA

Professor of Medicine, Division of General Medical Disciplines, Division of Infectious Diseases and Geographic Medicine, Stanford University

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

SYNOPSIS: In contrast to blood cultures obtained on therapy in patients with Gram-positive bacteremia and endocarditis, follow-up blood cultures in patients with Gram-negative bacteremia seldom provide useful information.

SOURCE: Canzoneri CN, Akhavan BJ, Tosur Z, et al. Follow-up blood cultures in Gram-negative bacteremia: Are they needed? *Clin Infect Dis* 2017;65:1776-1779.

In a retrospective study conducted at a large hospital in Houston, researchers studied 500 episodes of bacteremia to determine the frequency of follow-up blood cultures (FUBC) and assess risk factors for persistent bacteremia. Of the 500 episodes of bacteremia, 383 (77%) had at least one FUBC drawn. This included 54% of patients with initial bacteremia due to Gram-positive cocci (GPCs), 37% with bacteremia due to Gram-negative rods (GNRs), and 8% with polymicrobial bacteremia. Persistent bacteremia (defined as positive blood culture for the original organism at least 24 hours after the initial blood culture was drawn) was more common in GPC bacteremia (21%) than in polymicrobial (10%) or GNR bacteremia (6%). Duration of bacteremia was similar between groups (2.7-2.9 days). Positive FUBCs were most commonly *Staphylococcus aureus* (31), coagulase-negative *Staphylococcus* (six), *Enterococcus* (four), *Escherichia coli* (five), and *Klebsiella*, *Serratia*, and *Stenotrophomonas* (one each).

For all patients in the case series, factors shown to be predictive for positive FUBCs included fever on the day the FUBC was drawn, presence of a central catheter, and ESRD on hemodialysis. When broken down by persistent GPC vs. GNR bacteremia, fever, presence of a central catheter, DM, and ESRD on hemodialysis were present for GPC bacteremia, but only the presence of fever at the time the FUBC was drawn was predictive of persistent GNR bacteremia (six of eight patients).

The source of bacteremia was known in 273 (71%) patients who had FUBCs drawn. Only 37 had positive FUBCs. Broken down by source, the rate of positive FUBCs was quite low for most sources (UTI 3%, severe skin infection 6%, intra-abdominal infection 10%, osteomyelitis 0%, but higher for central catheter [34%] and pneumonia [15%].)

■ COMMENTARY

At our institution, FUBCs are ordered commonly, and when physicians are questioned about this practice,

they are surprised to learn that this is not considered standard of care. This relatively small study goes a long way toward illuminating that this is not a very helpful practice, especially in patients with GNR bacteremia who are doing well on appropriate antibiotics. (Overall, of the 140 patients with initial GNR bacteremia, it should be emphasized that only eight had positive FUBCs.) As the authors point out, not only does ordering routine follow-up blood cultures in patients with GNR bacteremia seldom produce helpful information, but common false-positive results can lead to longer length of stay, additional inappropriate antibiotic therapy, and increased healthcare costs. ■

ABSTRACT & COMMENTARY

Unexpected Benefit of Pneumococcal Vaccine in Decreasing the Burden of Otitis Media

By Patrick T. Kiessling and Philip R. Fischer, MD, DTM&H

Dr. Fischer is Professor of Pediatrics, Department of Pediatric and Adolescent Medicine, Mayo Clinic, Rochester, MN. Mr. Kiessling is a student at Mayo Clinic School of Medicine.

Dr. Fischer and Mr. Kiessling report no financial relationships relevant to this field of study.

SYNOPSIS: Surveillance data collected prospectively in Israel reveal a decline in progression from pneumococcal carriage to complex otitis media in both vaccine-targeted and non-vaccine serotypes following implementation of routine use of pneumococcal conjugate vaccines. Vaccinating against pneumococcal serotypes causing early-life infections may reduce the risk of subsequently developing complex otitis media due to other organisms.

SOURCE: Lewnard JA, Givon-Lavi N, Weinberger DM, et al. Pan-serotype reduction in progression of *Streptococcus pneumoniae* to otitis media after rollout of pneumococcal conjugate vaccines. *Clin Infect Dis* 2017;65:1853-1861.

Especially in infancy, *Streptococcus pneumoniae* is a major bacterial cause of otitis media (OM). Although originally licensed to combat invasive pneumococcal disease, pneumococcal conjugate vaccines (PCVs) target serotypes most commonly implicated in invasive disease but also show efficacy against vaccine-serotype OM. Most young children carry *S. pneumoniae* and other otopathogens, which can progress from colonization to symptomatic OM, including recurrent and nonresponsive infection. Reductions in OM incidence following rollout of PCV exceeded expectations, suggesting that PCVs affect the progression of both vaccine-targeted and non-vaccine serotypes. By preventing tissue damage sustained from early-life middle ear infections caused by vaccine-serotype pneumococci, PCVs may halt the cascade to complex OM from non-vaccine serotypes.

Pre-implementation studies of PCV demonstrated efficacy against complex OM, resulting in more than 30% reduction in the need for ventilation tubes. Further, rates of OM caused by *Moraxella catarrhalis*, non-typable *Haemophilus influenzae*, and *S. pyogenes* declined following PCV rollout, although the underlying mechanism behind these secondary benefits of vaccination is unknown. With this background information in mind, investigators in Israel attempted to further explore changes in progression from colonization to illness by analyzing pneumococcal carriage and complex OM incidence among Bedouin and Jewish children before and after PCV introduction.

Before and after introduction of PCV programs in southern Israel, investigators used the medical center that provided care to nearly all children in the region to collect data, and no changes in access to care occurred following vaccine implementation. Pneumococcal carriage prevalence before PCV implementation was measured in unvaccinated Jewish and Bedouin children either enrolled in a hepatitis A trial or a pre-implementation PCV dosing trial. Pneumococcal carriage prevalence after vaccine rollout was estimated by sampling Jewish and Bedouin children presenting to the emergency department with diagnoses unrelated to any potential pneumococcal carriage. OM incidence was measured by the number of episodes at this medical center necessitating middle ear fluid culture (primarily indicating complex OM), both before and after PCV

implementation. The progression rate was measured as the rate of OM incidence divided by carriage prevalence for each serotype.

Following PCV implementation, the incidence of middle ear fluid culture episodes from pneumococcal OM declined regardless of ethnicity. Rates of progression from carriage to OM in the first year of life decreased for PCV-targeted serotypes. For non-vaccine serotypes, the progression rate in the first year of life declined by 74% in Bedouin children and by 43% in Jewish children. The incidence of non-vaccine serotype OM decreased by 68% in Bedouin children younger than 12 months of age. Following vaccine rollout, no pneumococcal serotype demonstrated a statistically significant increase in progression. Therefore, the epidemiologic relationship between pneumococcal carriage and OM changed significantly following introduction of PCV. Damage sustained during early-life pneumococcal infections opens the door to less-virulent bacterial pathogens to progress to complex OM at older ages. Therefore, by inhibiting the establishment of early-life infection, vaccination against PCV serotypes may reduce overall complex OM burden.

■ COMMENTARY

Otitis media remains one of the most common infections seen in pediatric patients. A leading cause of both pediatric healthcare visits and pediatric antimicrobial prescribing in high-income countries, OM creates an estimated $2.88 billion in additional healthcare costs in the United States alone.[1,2] Close to 20% of children contract recurrent or persistent acute OM, while approximately one-third of acute OM infections are caused by *Streptococcus pneumoniae*, representing a significant burden on pediatric patients.[3,4] Pneumococcal conjugate vaccination is associated with protection against OM, coinciding with a continued decline in physician visits for acute OM, potentially representing a decreased burden of OM resulting from PCV rollout.[5]

The inspiration for this study stemmed from the desire to gain a greater understanding of the mechanism(s) by which pneumococcal vaccines exceeded impact predictions. PCV provided direct protection against progression of vaccine-targeted serotypes, as well as decreased progression rates for non-vaccine serotypes. Since vaccine-targeted serotypes primarily cause early-life infection, the subsequent reduction in non-vaccine serotypes following vaccine rollout revealed an unexpected relationship between early and later childhood pneumococcal infections.

Early-life pneumococcal infections cause damage and essentially stick a "foot in the door" to facilitate infection at older ages progressing to complex OM. This newfound relationship coincides with the "two-hit hypothesis" seen in other infectious diseases. Singly infected patients are made more susceptible to infection from a "hit" sustained by another infection. Epstein-Barr virus alone cannot cause endemic Burkitt lymphoma, but coinfection with *Plasmodium falciparum* malaria creates an environment suitable to this pediatric cancer.[6] Acute respiratory viral infections, such as influenza, facilitate conditions that allow pathogenic bacteria such as *Staphylococcus aureus* to invade and cause tracheitis.[7] Additionally, HIV infection predisposes susceptibility to infection by *Mycobacterium tuberculosis*, as well as progression from infection to active disease.[8] PCV prevented early "hits" from vaccine-targeted pneumococcal serotypes, and therefore established greater protection against non-vaccine serotypes that take advantage of the damage sustained by early-life pneumococcal infection.

The multifactorial nature of OM can be observed further in the differing responses to vaccine rollout seen in Bedouin and Jewish children. As reported in the paper by Lewnard, Bedouin children are subject to "larger family sizes, higher rates of overcrowding, and lower socioeconomic status." In the first year of life, Bedouin children exhibited higher OM incidence and higher pneumococcal carriage than their Jewish counterparts prior to vaccine rollout, perhaps related to some of these lifestyle issues. Then, following implementation of PCV, Bedouin children in the first year of life exhibited greater decreases in rates of progression from pneumococcal carriage to OM compared to Jewish children. During this time, they also experienced a decrease in the progression rate of serotypes not targeted by PCV that was nearly twice the decrease seen in Jewish children.

Not surprisingly, children at higher risk of pneumococcal disease demonstrated greater benefit from vaccination. Dysregulated inflammation of the middle ear can facilitate development and subsequent progression of OM.[9] Therefore, if lifestyle variations and medical interventions available to Jewish children limited middle ear inflammation, they may have decreased the susceptibility of Jewish children to pneumococcal carriage and OM infection. Thus, greater reductions in pneumococcal carriage and progression rates were observed in Bedouin children following PCV rollout. ■

REFERENCES

1. Rovers MM. The burden of otitis media. *Vaccine* 2008;26 Suppl 7: G2-4.
2. Ahmed S, Shapiro NL, Bhattacharyya N. Incremental health care utilization and costs for acute otitis media in children. *Laryngoscope* 2014;124:301-305.

3. Arrieta A, Singh J. Management of recurrent and persistent acute otitis media: New options with familiar antibiotics. *Pediatr Infect Dis J* 2004;23(Suppl 2): S115-S124.
4. Casey JR, Kaur R, Friedel VC, et al. Acute otitis media otopathogens during 2008 to 2010 in Rochester, New York. *Pediatr Infect Dis J* 2013;32:805-809.
5. Taylor S, Marchisio P, Vergison A, et al. Impact of pneumococcal conjugate vaccination on otitis media: A systematic review. *Clin Infect Dis* 2012;54:1765-1773.
6. Moormann AM, Snider CJ, Chelimo K. The company malaria keeps: How co-infection with Epstein-Barr virus leads to endemic Burkitt lymphoma. *Curr Opin Infect Dis* 2011;24:435-441.
7. Al-Mutairi B, Kirk V. Bacterial tracheitis in children: Approach to diagnosis and treatment. *Paediatr Child Health* 2004;9:25-30.
8. Pawlowski A, Jansson M, Sköld M, et al. Tuberculosis and HIV co-infection. *PLoS Pathog* 2012;8:e1002464.
9. Li JD, Hermansson A, Ryan AF, et al. Panel 4: Recent advances in otitis media in molecular biology, biochemistry, genetics, and animal models. *Otolaryngol Head Neck Surg* 2013;148(4 Suppl):E52-E63.

ABSTRACT & COMMENTARY

Prevention of *Clostridium difficile* Recurrence by Orally Administered Fecal Microbiota Transplantation

By Stan Deresinski, MD, FACP, FIDSA

Clinical Professor of Medicine, Stanford University

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

SYNOPSIS: Fecal microbiota transplantation orally administered in capsules was non-inferior to administration by colonoscopy.

SOURCE: Kao D, Roach B, Silva M, et al. Effect of oral capsule- vs colonoscopy-delivered fecal microbiota transplantation on recurrent *Clostridium difficile* infection: A randomized clinical trial. *JAMA* 2017;318:1985-1993.

In an unblinded, randomized, non-inferiority trial at three academic medical centers in Alberta, Canada, Kao and colleagues examined the relative efficacy of fecal microbiota transplantation (FMT) by colonoscopy or by orally administered capsules in prevention of recurrence of *Clostridium difficile* infection (CDI). The mean age of the 116 randomized (1:1) patients was 58 years. Two-thirds of the patients were women.

All patients were treated initially with oral vancomycin 125 mg four times daily for at least 10 days and until symptom resolution, followed by 125 mg twice daily, with discontinuation 24 hours before FMT. Patients were not allowed to take proton pump inhibitors. All patients ingested 4 liters of propylene glycol on the night prior to FMT. For patients randomized to colonoscopy, 360 mL of fecal slurry was delivered to the cecum, while those in the comparator group ingested 40 capsules containing fecal slurry. The slurry was prepared from stool provided by seven healthy volunteers.

The results of the two methods of treatment administration were identical with regard to the primary endpoint of prevention of recurrence at 12 weeks after a single FMT: 51/53 (96.2%) and 50/52 (96.2%) in the capsule and the colonoscopy groups, respectively. Both methods were tolerated; non-serious adverse events occurred in 5.4% and 12.5%, respectively.

■ COMMENTARY

The authors point out that the success rates in this study were higher than previously reported. They suggest that this may be the consequence of at least two factors — the fecal dose and the intestinal washout. Thus, the amount of feces delivered in this study was greater than that in others. Vancomycin persists in the fecal stream for as long as eight days after completion of a course of oral administration, and the intestinal washout can be hypothesized to remove residual vancomycin, the persistence of which would adversely affect the fecal microbiota.

This study is valuable because it demonstrates that previous studies that found somewhat better outcomes with FMT by colonoscopy than via the upper gastrointestinal tract may not be correct. The ability to avoid colonoscopy makes the overall cost of FMT significantly lower and, with the commercial availability of orally administered transplant material (although not studied here), makes FMT more widely available. How this approach fares when compared to others, such as the use of fidaxomicin and vancomycin tapers, remains to be determined in additional randomized trials. ■

PHARMACOLOGY UPDATE

Zoster Vaccine Recombinant Adjuvanted (Shingrix)

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

Dr. Elliott is Assistant Clinical Professor of Medicine, University of California, San Francisco.

Dr. Chan is Associate Clinical Professor, School of Pharmacy, University of California, San Francisco.

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

The FDA has approved a second zoster vaccine for the prevention of shingles in adults. In contrast to the first vaccine (Zostavax), which is a live attenuated vaccine (ZVL), zoster vaccine recombinant adjuvanted is non-live and comprised of the surface glycoprotein E antigen component (HZ/su). This vaccine is marketed as Shingrix.

INDICATIONS

HZ/su is indicated for the prevention of herpes zoster (shingles) (HZ) in adults ≥ 50 years of age.[1]

DOSAGE

The recommended dose is 0.5 mL given intramuscularly at zero and two to six months.[1] HZ/su is available as a single-dose vial of lyophilized varicella zoster virus glycoprotein E antigen component to be reconstituted with the accompanying vial of AS01B adjuvant suspension component.

POTENTIAL ADVANTAGES

HZ/su is more effective than ZVL in vaccine efficacy.

POTENTIAL DISADVANTAGES

HZ/su requires two injections, compared to a single dose for ZVL. There is potential for reduced adherence with the second dose.

COMMENTS

Efficacy was evaluated in two randomized, placebo-controlled, observer-blind clinical studies.[1,2] Study 1 included subjects ≥ 50 years of age. Study 2 included subjects ≥ 70 years of age. In study 1, subjects were randomized to HZ/su or placebo and stratified by age: 50-59, 60-69, 70-79, and ≥ 80 years. The researchers excluded immunocompromised subjects, those with a history of previous herpes zoster, or those who were vaccinated against varicella or HZ. Subjects were followed for a median of 3.1 years. The primary endpoint was confirmed cases of HZ. In an analysis population of 14,759 subjects, HZ/su reduced the risk of developing HZ by 97.2%, with no clear differences among the age stratum. No cases of postherpetic neuralgia (PHN) were reported in the vaccine group, compared to 18 in the placebo group. Study 2 randomized subjects 70-79 and ≥ 80 years to HZ/su or placebo with a median follow-up of 3.9 years. In an analysis cohort of 13,163 subjects, vaccine efficacy was 89.8%. Pooled data from the two studies showed vaccine efficacy of 91.3% for those ≥ 70 years of age. There were four cases of PHN in the vaccine group vs. 36 in the placebo group. The efficacy of HZ/su is more effective than reported with ZVL. A review of three large retrospective, nested, case-control studies totaling approximately 2.4 million mainly immunocompetent subjects showed a real-world effectiveness of ZVL of 48-55% in reducing the incidence of HZ and 59-62% in reducing postherpetic neuralgia.

In an open-label study, there was no interference reported between HZ/su and a quadrivalent influenza vaccine (Fluarix).[1] In patients with a prior history of herpes zoster, HZ/su has been shown to induce immune response of 90% (95% confidence interval, 82-96%) based on anti-glycoprotein E antibodies one month after the second dose.[5] In adults previously vaccinated with ZVL, immune response to HZ/su was noninferior to those previously not vaccinated.[6] The most common adverse reactions associated with HZ/su are pain, redness, and swelling at the injection site. Others include muscle pain, tiredness, headache, shivering, fever, and upset stomach.[1]

CLINICAL IMPLICATIONS

Shingles is caused by the reactivation of dormant varicella zoster virus. Older individuals are at higher risk because of the reduced ability of the immune system to prevent activation. The disease usually occurs between ages 50-79 years, with an overall incidence of 2.0-4.6 cases per 1,000 person-years and increases to 10-12.8 per 1,000 person-years in

those ≥ 80 years of age.[2,7] Postherpetic neuralgia is a complication of shingles that occurs in 20% of cases in individuals between 60-65 years of age and approximately 30% in those > 80 years of age.[7] HZ/su offers a more effective vaccine and is recommended by the Advisory Committee on Immunization Practices for the prevention of herpes zoster and related complications for immunocompetent adults ≥ 50 years of age, for adults who previously received Zostavax, and is preferred over Zostavax.[8] The cost for Shingrix is $280 for two doses. ■

REFERENCES

1. Shingrix Prescribing Information. GlaxoSmithKline Biologicals, October 2017.
2. Cunningham AL, Lal H, Kovac M, et al. Efficacy of the herpes zoster subunit vaccine in adults 70 years of age or older. *N Engl J Med* 2016;375:1019-1032.
3. Ansaldi F, Trucchi C, Alicino C, et al. Real-world effectiveness and safety of a live-attenuated herpes zoster vaccine: A comprehensive review. *Adv Ther* 2016;33:1094-1104.
4. Zostavax Prescribing Information. Merck & Co., Inc, May 2017.
5. Godeaux O, Kovac M, Shu D, et al. Immunogenicity and safety of an adjuvanted herpes zoster subunit candidate vaccine in adults ≥ 50 years of age with a prior history of herpes zoster: A phase III, nonrandomized, open-label clinical trial. *Hum Vaccin Immunother* 2017;13:1051-1058.
6. Grupping K, Campora L, Douha M, et al. Immunogenicity and safety of the HZ/su adjuvanted herpes zoster subunit vaccine in adults previously vaccinated with a live-attenuated herpes zoster vaccine. *J Infect Dis* 2017 Sep 26. doi: 10.1093/infdis/jix482. [Epub ahead of print].
7. Fashner J, Bell AL. Herpes zoster and postherpetic neuralgia: Prevention and management. *Am Fam Physician* 2011;83:1432-1437.
8. American Academy of Family Physicians. ACIP Recommends New Herpes Zoster Subunit Vaccine, Oct. 31, 2017. Available at: http://bit.ly/2hIRPrb. Accessed Nov. 22, 2017.

Infectious Disease [ALERT]

Updates

By Carol A. Kemper, MD, FACP

The Origins of Smallpox Vaccine Virus

The origins of vaccinia virus, used for smallpox vaccination, have long been debated. For years, many believed that cowpox virus was the source for vaccinia virus, ever since British surgeon Edward Jenner from Berkeley, Gloucestershire, first published accounts in 1798 and 1799 regarding the use of cowpox virus for scarification to generate protective immunity (ostensibly following observations that milkmaids were less likely to succumb to smallpox). However, it has been recognized for years that vaccinia virus differs from cowpox virus (CPXV), and the exact origins for the vaccine virus have remained a mystery. Complicating matters is the fact that various smallpox vaccines were manufactured in different countries and remained in use for more than a century before the World Health Organization (WHO) standardized the vaccine in 1967 using four different strains of vaccinia virus.

A sample of 1902 smallpox vaccine manufactured by H.K. Mulford Co., an American company in Philadelphia, was recently discovered. DNA extracted from the vaccine was submitted to whole genome amplification and compared with 65 other published genome orthopoxvirus sequences.[1] Contrary to the cowpox theory, the 1902 vaccinia virus most closely resembles horsepox virus (99.7%), using different phylogenetic algorithms. Interestingly, deletions found at each end of the vaccine strain were not observed in either natural cowpox or horsepox viruses, but were similar to current vaccinia strains.

This suggests that horsepox, and not cowpox, may have served as the progenitor virus for vaccinia virus. In actuality, orthopox viruses are known to infect many different animals, and horsepox virus and CPXV are very similar, and probably originally derived from rodent poxvirus, which serves as a reservoir for cowpox infection. Further, an earlier study observed that CPXV is not a single species but a composite of different strains of virus (up to five) that can infect cows, other animals, and (accidentally) humans.

Carroll and colleagues examined whole genome sequences of CPXV in 2011, creating a phylogenetic tree, with comparisons to other animal orthopoxviruses.[2] CPXV fell into two major clades, one of which contained strains of virus from the United Kingdom and Germany. The other clade contained a group of viruses including buffalopox (from India), horsepox, rabbitpox, and CPXV strains found in Finland and Austria. CPXV isolates from Germany, most of which came from accidental infection of humans, showed more genetic variability than those from the United Kingdom, suggesting independent evolution and, possibly, different rodent reservoirs. In reviewing that phylogenetic tree, horsepox virus certainly appears most closely related

to three different strains of vaccine-derived vaccinia virus.

Horsepox virus apparently no longer exists in nature, although samples of horsepox virus are maintained at the CDC. In 2006, scientists in New York published the sequence of horsepox virus, derived from a wild strain recovered 40 years earlier from horses in Mongolia.

Orthopox viruses have fairly sizeable genomes, and both CPXV (averaging 230 kb pairs) and horsepox virus (~212 kb pairs) are about 30 kb pairs larger than vaccinia virus — and 30 times larger than poliovirus. Discord occurred in 2017 when a Canadian researcher, using DNA sequences purchased from a German company, was able to recreate horsepox virus.[3] Apparently, he had applied to the CDC for samples of horsepox virus, but was declined — so decided to make his own. Both the United States and the WHO prohibit the production of variola (smallpox) virus, and researchers are not allowed to recreate more than 20% of the variola genome. It has been hoped that no one would try — or that it would not be so readily possible. The United States maintains a list of 15 "dual-use" agents, including smallpox virus, for which research and production are restricted, but horsepox is not included on this list. Nonetheless, the implication of the Canadian work is obvious. As one researcher put it, "No question, if it's possible with horsepox, it's possible with smallpox."

Meanwhile, the exact origins of Jenner's "vaccine" are becoming somewhat less of a mystery. All of this genomic work strengthens the likelihood that horsepox may be the progenitor for the original vaccinia virus. Earlier WHO reports of the origins of vaccinia virus in 1988 suggested that many physicians, including Jenner, likely turned to horsepox, rather than cowpox, for scarification. For one, cowpox virus was available only sporadically — and physicians at the time may have substituted horsepox as needed. They even may have thought they were the same virus. But one of the best parts of researching this article was the term used for inoculation of horsepox virus — "equination" — as in "equinate your kids," (although that equination has taken on new meaning with online horse racing).

REFERENCES

1. Schrick L, Tausch SH, Dabrowski PW, et al. An early American smallpox vaccine based on Horsepox. *N Engl J Med* 2017;377:1491-1492.
2. Carroll DS, Emerson GL, Li Y, et al. Chasing Jenner's vaccine: Revisiting cowpox virus classification. *PLoS One* 2011;6:e23086.
3. Kupferschmidt K. How Canadian researchers reconstituted an extinct poxvirus for $100,000 using mail-order DNA. *Science* 2017; July 6.

No More Fun Helping Mommy Bake

SOURCE: Crowe SJ, Bottichio L, Shade LN, et al. Shiga toxin-producing *E. coli* infections associated with flour. *N Engl J Med* 2017;377:2036-2043.

Being a kid just isn't as much fun as it used to be. One of my favorite things growing up was getting to lick the bowl whenever mom made a cake. And, my mother and my grandmother used to set aside time every few months to make 50-60 pie crusts for the freezer, yielding plenty of extra pie dough to play with and nibble on. Food safety experts now warn against this practice.

While some home cooks may recognize raw eggs as a potential source for *Salmonella* and *Campylobacter* infection, few would suspect flour as a source for serious infection. It sits on the shelf for months, it looks clean, white, and innocuous — and it's dry. Not the usual medium one would imagine for a food-borne illness.

In 2016, a multi-state outbreak of Shiga toxin-producing *Escherichia coli* (STEC) serogroups O121 and O26 occurred, resulting in a total of 63 infections in 24 states within the United States and Canada. Seventeen people required hospitalization. Many of those affected clustered within families, suggesting a common source for infection. STEC typically causes a gastroenteritis with abdominal cramping and bloody diarrhea. A minority of those infected, especially children younger than 5 years of age, may develop the more serious complication of hemolytic-uremic syndrome.

As soon as the outbreak was recognized, a multijurisdictional investigation was launched. Conditional logistic-regression analysis suggested that the infection was related to the use of a single brand of flour. The investigation quickly pointed to a single manufacturer of flour from one manufacturing facility in Kansas City. The organism was isolated from flour samples, and whole genome sequencing of clinical isolates and strains isolated from food samples proved they were closely related. Tasting or handling unbaked cookie dough or uncooked batter proved to be the culprit activity. Multiple step-wise recalls of flour ensued, resulting in the eventual destruction of 10 million pounds of flour, including unbleached, all-purpose, and self-rising flours, from this single facility.

The CDC and the FDA offer several tips for avoiding food-borne illness:

- Do not eat raw cookie dough, cake mix, batter, or any other dough or mix that should be baked or cooked.
- Keep raw food separate from other foods while preparing them — and keep in mind that dry flour

can spread easily when sifting or mixing.
• After contact with raw foods, wash hands, work surfaces, and utensils well with good soap and water.
• Restaurants and preschools should not allow children to play with raw dough.

Annual Influenza Vaccination of Physicians

SOURCE: California Department of Public Health. Healthcare-Associated Infections Program. Healthcare Personnel Influenza Vaccination in California Hospitals. Nov. 14, 2017. Available at: https://www.cdph.ca.gov/Programs/CHCQ/HAI/Pages/HealthcarePersonnelInfluenzaVaccinationReportingInCA_Hospitals2015_2016.aspx. Accessed Dec. 11, 2017.

To help achieve the CDC Healthy People 2020 goal and reduce healthcare-associated illness, many counties within California launched a goal to achieve 90% or better vaccination of healthcare workers beginning in 2011-2012. Thirty-five counties in the state, including our own, have issued a public health order requiring unvaccinated healthcare providers to wear a mask whenever working in clinical areas during flu season. Since the introduction of these county mandates, influenza vaccination of healthcare personnel has increased steadily from 63% in 2010-2011 to 83% in 2016-2017. The highest rates of compliance (87%) were observed in paid employees of hospitals, while the lowest rates (67%) were observed among licensed independent practitioners, including physicians and physician assistants, not directly paid by a hospital. Influenza vaccination of licensed independent practitioners in 2016-2017 plateaued and even slightly fell compared with earlier influenza seasons.

Almost one-third of California counties have achieved a > 90% vaccination rate across all healthcare provider groups. Reported influenza vaccine rates for healthcare personnel working within the 35 California counties with a county mandate (84%) were higher than those working in one of the 20 counties without a mandate (81%).

Hospitals throughout the United States now are required to collect data for annual influenza vaccination for all healthcare personnel working within their facility, paid or otherwise, and report these data to the National Healthcare Safety Network using their secure, web-based system. To achieve the 90% goal, developing additional strategies to improve influenza vaccination rates is important.

For one thing, California state law requires acute care hospitals to offer influenza vaccination at no cost to all healthcare personnel. For another, California hospitals are required to provide an attestation/declination form to all healthcare personnel working within their facility. Our community-based hospital offers a badge decal to physicians upon proof of vaccination. But how do you best monitor and enforce this process? What "teeth" do community hospitals have, especially in counties or states without such a mandate? And how do you get community-based physicians to submit proof of their voluntary vaccination, short of threatening resumption of their hospital staff privileges?

[Since the introduction of these county mandates, influenza vaccination of healthcare personnel has increased steadily from 63% in 2010-2011 to 83% in 2016-2017.]

While the California Department of Public Health report suggests that independent physicians vaccine rates lag behind paid employees, I suspect this is largely due to a gap in voluntary physician reporting. For example, in our hospital, thus far only 17% of physicians have returned their attestation form for the current influenza season (and which physician in their right mind would voluntarily provide a declination?). My guess is that most have been vaccinated.

Hospitals are already squeezed to improve patient safety in myriad ways — and financially penalized if they fall short. For a community-based hospital to find the FTE to track down forms for 1,600 physicians is no small task. It's easy for authorities to draft laws and issue mandates, but then adequate bonus funding should be provided for hospitals to perform this task successfully. ■

CME INSTRUCTIONS

To earn credit for this activity, please follow these instructions:
1. Read and study the activity, using the provided references for further research.
2. Log onto AHCMedia.com and click on My Account. *First-time users must register on the site.*
3. Pass the online tests with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.
4. After successfully completing the test, a credit letter will be emailed to you instantly.
5. Twice yearly after the test, your browser will be directed to an activity evaluation form, which must be completed to receive your credit letter.

CME QUESTIONS

1. In Israel, routine pneumococcal vaccination of children:

a. led to decreased nasopharyngeal carriage of vaccine-targeted strains.

b. led to decreased progression to disease by vaccine-targeted strains.

c. led to decreased progression to disease by non-vaccine-targeted strains.

d. All of the above

2. Which of the following is correct regarding the randomized trial by Kao et al examining the prevention of recurrence of *Clostridium difficile* infection by fecal microbiota transplantation (FMT)?

a. Oral administration of FMT was not inferior to colonoscopic delivery to the cecum.

b. The key to success was the continuation of vancomycin during the transplantation.

c. Use of intestinal washout reduced efficacy regardless of the route of FMT delivery.

d. Oral administration was very poorly tolerated.

3. Which of the following is the single best answer regarding Zostavax and Shingrix?

a. Zostavax contains live attenuated virus while Shingrix contains a recombinant surface glycoprotein.

b. Shingrix is superior to Zostavax in the prevention of herpes zoster.

c. Shingrix is superior to Zostavax in the prevention of postherpetic neuralgia.

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.