RELIAS MEDIA

Vol. 39, Issue 11, August 2020
ReliasMedia.com

Infectious Disease [ALERT]

Incisive Commentary and Clinical Abstracts on Current Issues in Infectious Diseases

ABSTRACT & COMMENTARY

COVID-19: Lessons from Spring Break

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: A high rate of COVID-19 occurred as the result of an outbreak in spring breakers. Rapid recognition and intervention, as well as the youth and good health of those infected, was effective in limiting the adverse consequences.

SOURCE: Lewis M, Sanchez R, Auerbach S, et al. COVID-19 outbreak among college students after a spring break trip to Mexico — Austin, Texas, March 26-April 5, 2020. *MMWR Morb Mortal Wkly Rep* 2020;69:830-835.

The COVID-19 Center at the University of Texas at Austin recognized the possibility of a COVID-19 outbreak on March 28, 2020, after becoming aware of just three confirmed infections in symptomatic students. Contact tracing, initiated on the same day, identified a spring break trip to Cabo San Lucas, Mexico, during March 14-19, as the likely initial transmission event. The center rapidly trained medical and public health students, as well as clinical and research staff members, to extend contact tracing. After reaching travelers to Cabo San Lucas and their known contacts by text, they conducted phone interviews and offered SARS-CoV-2 testing to symptomatic testing individuals (testing was limited by availability) and asked them to self-isolate until test results were reported to be negative or, if positive, to follow Centers for Disease Control and Prevention (CDC) isolation recommendations. Asymptomatic travelers and contacts were advised to monitor symptoms and to self-quarantine for 14 days.

Of the 231 subjects tested, 64 (28%) had positive results, including 60 of 183 (33%) travelers to Cabo San Lucas. In addition, one of 13 (8%) household contacts of travelers and three of 35 (9%) community contacts of travelers also had positive tests. Of the 64 with positive tests, 14 (22%) were asymptomatic at the time of testing and only six

Financial Disclosure: Peer Reviewer Patrick Joseph, MD, is a consultant for Genomic Health Reference Laboratory, Siemens Clinical Laboratory, and CareDx Clinical Laboratory. *Infectious Disease Alert*'s Editor Stan Deresinski, MD, FACP, FIDSA, Updates Author Carol A. Kemper, MD, FACP, Peer Reviewer Kiran Gajurel, MD, Executive Editor Shelly Morrow Mark, Editor Jason Schneider, and Editorial Group Manager Leslie Coplin report no financial relationships to this field of study.

[INSIDE]

Daptomycin Plus a β-Lactam Compared to Daptomycin Alone for MRSA Bacteremia page 124

Rotavirus Vaccine Is Safe and Effective page 125

Immunomodulatory Treatment of Disseminated Coccidioidomycosis page 127

Infectious Disease [ALERT]

Infectious Disease Alert, (ISSN 0739-7348), is published monthly by Relias LLC, 1010 Sync St., Ste. 100, Morrisville, NC 27560-5468. Periodicals postage paid at Morrisville, NC, and additional mailing offices. POSTMASTER: Send address changes to *Infectious Disease Alert*, Relias LLC, 1010 Sync St., Ste. 100, Morrisville, NC 27560-5468.

GST Registration Number: R128870672.

This is an educational publication designed to present scientific information and opinion to health professionals to stimulate thought and further investigation. It does not provide advice regarding medical diagnosis or treatment for any individual.

SUBSCRIBER INFORMATION
(800) 688-2421
customerservice@reliasmedia.com
ReliasMedia.com

Editorial Email:
mmark@relias.com

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

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

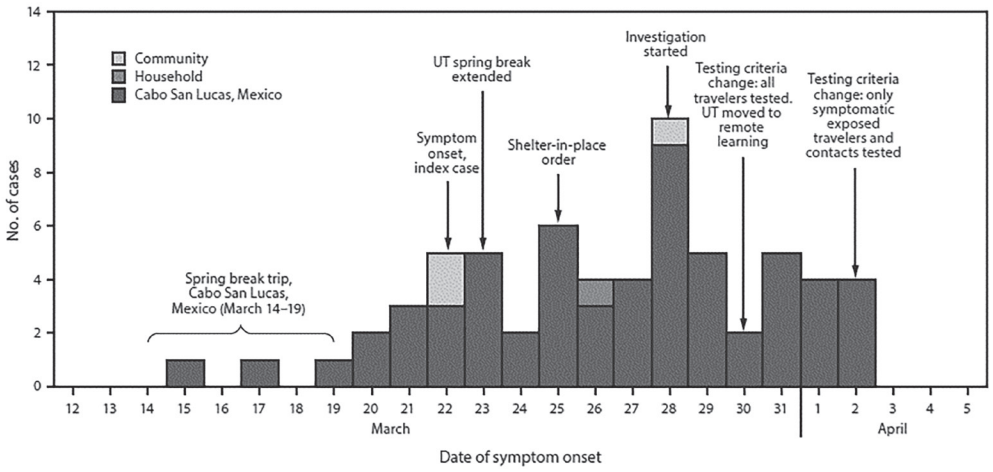
Relias LLC designates this enduring material for a maximum of ***3*** *AMA PRA Category 1 Credits*™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

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.

Figure 1: COVID-19 Cases (n = 64) Following a Spring Break Trip to Cabo San Lucas, Mexico, by Exposure Source and Date of Symptom Onset,* and Public Health Investigation — Austin, Texas, March 12 – April 5, 2020



Abbreviations COVID-19 = coronavirus disease 2019; UT = University of Texas.
* For asymptomatic cases, date of testing is used as a proxy for date of symptom onset.
Source: Lewis M, Sanchez R, Auerbach S, et al. COVID-19 outbreak among college students after a spring break trip to Mexico — Austin, Texas, March 26-April 5, 2020. *MMWR Morb Mortal Wkly Rep* 2020;69:830-835.

(11%) reported fever. Half of those with negative tests reported symptoms; 9% had fever. Nonetheless, the presence of symptoms was associated with a greater risk of having a positive test than was being asymptomatic (odds ratio [OR] = 3.5; 95% confidence interval [CI], 1.8 to 7.4), although no particular grouping of symptoms was diagnostic of COVID-19.

These results are enlightening, although as pointed out by the authors, a number of restraints may have affected their accurate rendering of the outbreak. Among these was an incomplete knowledge of the clinical performance characteristics of the commercial polymerase chain reaction (PCR) test that was used, which, however, has an analytic sensitivity (think "spiked" samples) of 95% in detecting 48 viral RNA copies. Another was the fact that testing could be performed only once because of supply shortages.

The foresight of the University of Texas at Austin to have in a place a COVID-19 center is to be commended, as is their rapid recognition of an outbreak and just as rapid deployment of resources to attack it with delegated authority from the public health department. (*See Figure 1.*) Their ability to rapidly train and deploy individuals for contact tracing also was remarkable. Their swift action undoubtedly limited the number of cases of infection that would have occurred in its absence. As a result, the consequences of this outbreak were limited.

However, other factors also were at play in limiting the damage. None of the 64 infected subjects were hospitalized and none died, having been spared by youth and previous good health.

Thus, among those tested, the median age was only 22 years (range, 19-62 years), and only 15 (8%) had an underlying medical condition. Fortunately, older adults do not often have the same spring break rituals. ■

We'd Love to Hear from You!

We're always looking for ways to do better! Please take five minutes to complete our annual user survey (https://bit.ly/2XYHWdM), and we'll enter you to win a yearlong subscription to Relias Media.

ABSTRACT & COMMENTARY

COVID-19 in Early Infancy

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: An evaluation of 18 infants with COVID-19 in the first three months of their lives found that the illness generally was not severe despite the presence of very high viral loads.

SOURCE: Mithal LB, Machut KZ, Muller WJ, Kociolek LK. SARS-CoV-2 infection in infants less than 90 days old. *Pediatrics* 2020; doi: 10.1016/ j.jpeds.2020.06.047

Mithal and colleagues retrospectively identified infants younger than 90 days of age with positive SARS-CoV-2 real-time polymerase chain reaction (RT-PCR) tests at the Ann & Robert Lurie Children's Hospital in Chicago from April 11 to May 12, 2020. During that time, testing was performed on all children in whom COVID-19 was considered because of symptoms, as well as all asymptomatic patients as part of routine screening at the time of hospital admission or before procedures. Testing was performed at a variety of sites, including a drive-through center, the emergency department and other ambulatory settings, intensive care units, and the general inpatient setting.

Of the 171 infants tested, 18 (10%) were positive; none had a significant past medical history. Fifteen of the 18 were tested in the emergency department and three were tested in outpatient settings. Fever was present in 14 (77.8%), while two had cough as their sole symptom. One had choking with feeding, and one, who was screened because the parents were infected, was asymptomatic. Fourteen (78%) had close contacts and/or family members with symptoms consistent with COVID-19.

Half of the infants were admitted to the general inpatient service and none subsequently required intensive care. The reasons for admission included clinical observation, evaluation of feeding tolerance, and empiric intravenous antibiotics.

Eight of the nine admitted had fever, while four had cough or tachypnea, four had poor feeding, three had vomiting, and one developed diarrhea after admission. None were hypoxic, and the chest radiograph was normal in all five in whom this was performed. Empiric intravenous antibiotics were administered to six patients, but only one had a documented bacterial infection that involved the urinary tract. None of the five tested for other viral infections had a positive test.

■ COMMENTARY

The results of this study indicating relatively mild illness in young infants with COVID-19 are consistent with similar reports. This was true in the experience reviewed here despite evidence that the infants had a very high viral load. The RT-PCR cycle threshold (ct) is a reflection of the amount of virus present — low values, meaning fewer replication cycles are necessary for viral detection, are consistent with high viral loads. While the ct values of positive control samples in the testing in the presence of 1,000 copies per mL was 22.9 ± 0.4, the values for 14 of the infants ranged from 3.00-6.58, indicating very high viral loads.

COVID-19 testing must now be a part of the evaluation of infants with fever as well as various other symptoms suggestive of a possible infectious illness, including very subtle ones. ■

ABSTRACT & COMMENTARY

Outcomes with Daptomycin Plus a β-Lactam Compared to Daptomycin Alone for MRSA Bacteremia

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

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

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

SYNOPSIS: In a retrospective cohort study, investigators found the addition of a β-lactam antibiotic to daptomycin led to less clinical failure (60-day all-cause mortality and/or 60-day recurrence) in patients with methicillin-resistant *Staphylococcus aureus* bacteremia.

SOURCE: Jorgensen SCJ, Zasowski EJ, Trinh TD, et al. Daptomycin plus β-lactam combination therapy for methicillin-resistant *Staphylococcus aureus* bloodstream infections: A retrospective, comparative cohort study. *Clin Infect Dis* 2020;71:1-10.

Methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia causes significant morbidity and mortality despite the availability of antibiotics that demonstrate good in vitro activity. Thus, the optimal treatment of MRSA bacteremia remains unclear. Based on data from smaller studies and case reports, Jorgensen and colleagues sought to determine whether the combination of daptomycin plus a β-lactam antibiotic improved outcomes for MRSA bacteremia compared to daptomycin alone.

The study was a retrospective, observational, cohort study conducted at two medical centers in Detroit. Inclusion criteria were age 18 years and older, one or more blood cultures positive for MRSA, and daptomycin started within 120 hours of initial blood culture collection and continued for at least 72 hours. Patients who received any β-lactam for at least 24 hours and within 24 hours of the initiation of daptomycin were included in the daptomycin plus β-lactam group. Patients who had a pulmonary source for their MRSA bacteremia or cases of polymicrobial bacteremia were excluded. The authors adjusted for confounding variables by employing an inverse probability treatment weighting approach.

There were 157 patients in the daptomycin monotherapy group and 72 patients in the daptomycin plus β-lactam group. The groups were mostly well balanced, although heart failure and chronic kidney disease were more prevalent in monotherapy recipients. Moreover, a greater proportion of patients who received combination therapy had an osteoarticular or skin source as the etiology of their MRSA bacteremia, while an intravenous (IV) catheter-related bacteremia was a more common source in the monotherapy group. Most (61%) were treated initially with vancomycin and were switched to daptomycin because of a vancomycin minimum inhibitory concentration (MIC) of 2 mg/L. The reasons for adding the β-lactam drug included empirical coverage (45.8%), anticipated synergy (34.7%), or another concurrent infection (19.4%). The most commonly used β-lactam agents were cephalosporins (cefepime n = 31 [43%], cefazolin n = 18 [25%], ceftaroline n = 7 [9.7%], and ceftriaxone n = 7 [9.7%]). Of the 52 patients who experienced clinical failure, 43 were in the monotherapy group and nine were in the combination group (P = 0.013). There was a significant reduction in the odds of clinical failure in the combination group vs. the monotherapy group (adjusted odds ratio [aOR] 0.386; 95% confidence interval [CI], 0.175-0.853).

Acute kidney injury (AKI) was significantly higher in the combination group compared to the monotherapy group (10.8% vs. 2.9%, respectively; P = 0.046). Nine of the 10 patients in the monotherapy group who developed AKI received at least one dose of a nephrotoxic drug within 72 hours prior to the onset of AKI. There were six reported cases of *Clostridioides difficile* infection, four in the combination group and two in the monotherapy group (P = 0.08). Finally, creatinine phosphokinase elevation occurred in 10 patients, which was not significantly different between the two groups.

■ COMMENTARY

The argument for and against combination therapy for MRSA bacteremia has long been debated. The study by Jorgensen and colleagues adds to the

evidence base on combination therapy and likely will be cited often in future studies. However, it raises about as many questions as it answers. On one hand, combination therapy was associated with significantly reduced 60-day mortality and/or 60-day recurrence of MRSA bacteremia. On the other hand, significantly more AKI occurred in the combination therapy group, despite a lower baseline proportion of patients with chronic kidney disease (CKD) compared to the monotherapy group. Moreover, when the 60-day mortality and/or 60-day recurrence measurement was divided further into 60-day mortality, 30-day mortality, 60-day recurrence, and 30-day recurrence, there were no significant differences between the combination and monotherapy groups.

Both the authors and an accompanying editorial raise an important issue from the recent CAMERA2 study.[1] This randomized clinical trial for MRSA bacteremia compared monotherapy (vancomycin or daptomycin) to combination therapy (vancomycin or daptomycin plus seven days of an antistaphylococcal penicillin or cefazolin). It was stopped early after an interim analysis found no effect on death or complications at 90 days, but a four-fold increase in AKI among patients who received combination therapy.[2] Notably, patients who received cefazolin had a lower rate of AKI (7%) compared to those who received flucloxacillin (35%).

Should all patients with MRSA bacteremia receive combination therapy? The short answer is no. In the vast majority of instances, in vitro and observational studies should not be relied on for making clinical decisions. It has become evident, based on the study by Jorgensen and colleagues and previous ones such as CAMERA2, that additional antibiotics increase the risk for adverse events. Thus, while there is a suggestion of benefit, it currently is not enough to recommend that combination therapy be used in most cases of MRSA bacteremia.

This is a good example of where definitive randomized trials, in addition to CAMERA2, are needed. Indeed, the addition of cefazolin to vancomycin or daptomycin might be safer than other β-lactams, and it seems reasonable to investigate this hypothesis. Another important goal will be to identify subgroups of patients for whom the benefits of combination therapy outweigh the risks. Until then, the debate over combination therapy will remain unsettled. ■

REFERENCES

1. Holland TL, Davis JS. Combination therapy for MRSA bacteremia: To β or not to β? *Clin Infect Dis* 2020;71:11-13.
2. Tong SYC, Nelson J, Paterson DL, et al. CAMERA2 - Combination antibiotic therapy for methicillin-resistant *Staphylococcus aureus* infection: Study protocol for a randomised controlled trial. *Trials* 2016;17:170.

ABSTRACT & COMMENTARY

Rotavirus Vaccine Is Safe and Effective

By Philip R. Fischer, MD, DTM&H

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

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

SYNOPSIS: Routine rotavirus vaccination of infants, when implemented broadly, is safe and is associated with reductions in diarrhea-related hospitalizations, mortality, and morbidity (such as malnutrition) in children.

SOURCE: Marquis A, Koch J. Impact of routine rotavirus vaccination in Germany: Evaluation five years after its introduction. *Pediatr Infect Dis J* 2020;39:e109-e116.

Two live attenuated, oral rotavirus vaccines became available in Germany in 2006, a time when rotavirus was the most common cause of gastroenteritis in preschool-age children and when rotavirus accounted for approximately 20,000 hospitalizations each year. However, there was concern that rotavirus vaccine increased the risk of intussusception, especially in older infants, so vaccination was initiated by the 12th week of life. Rotavirus vaccination became part of the standard immunization program in 2013, and Marquis and Koch looked back on outcomes of routine vaccination after five years of the use of these vaccines.

During the first five years of routine rotavirus immunization of infants in Germany, coverage by vaccination reached 80% of infants. The incidence of documented outpatient rotavirus gastroenteritis in preschool-age children dropped by 74% to 194 per 100,000 population, and the incidence of rotavirus-related hospitalizations dropped 70%. The

improvements were most notable in the youngest age groups. The incidence of rotavirus infection also dropped in children who were too old to receive vaccination, suggesting some protection via herd immunity. Interestingly, the winter season of rotavirus infections shifted with vaccination to begin six weeks later.

There was no evidence for an increase in rotavirus disease in older populations, indicating that vaccination did not merely delay the onset of risk of becoming ill with rotavirus. With widespread rotavirus immunization in Germany, the incidence of intussusception during the first year of life actually dropped 28% ($P < 0.001$) to 48 per 100,000 children.

■ COMMENTARY

With so much bad health news in the world these days and with so much societal pressure for a new coronavirus vaccine, it is nice to be reminded of some good news. Routine vaccination works.

This new report from Germany represents valuable post-marketing evaluation of the vaccine and its programmatic implementation. As such, it is useful. Indeed, initial post-marketing evaluation of an earlier rotavirus vaccine revealed an increased risk of intussusception.[1] The current vaccine and program being used in Germany has now been shown to be safe and effective. Routine rotavirus vaccination in Germany was associated with decreased incidences both of outpatient and inpatient rotavirus illnesses. The vaccine also was safe in a large population-level follow-up and was not associated with increased later-life rotavirus infections, suggesting mere delays in disease acquisition. Not only was there not an increased risk of intussusception, but vaccination also seemed to protect against intussusception.

Rotavirus was isolated and identified as a cause of childhood diarrhea in 1969.[2] Since 2006, four live attenuated, oral rotavirus vaccines have been developed and used around the world.[2] Overall, 107 countries have rotavirus vaccination programs, but 90 countries still do not have programs for routine rotavirus vaccination.[2]

Gastroenteritis is a significant cause of childhood death worldwide, and rotavirus-related diarrhea still accounts for huge cost, morbidity, and even some mortality in the United States. Initial rotavirus vaccine efforts were compromised with the finding of an increased risk of life-threatening intussusception after vaccination. Newer rotavirus vaccines, as seen in the study in Germany, do not have that problem.

Rotavirus vaccination is part of the current American routine childhood immunization series. Different rotavirus vaccines are made with different strains of human and bovine rotavirus antigens.[1] Based on risks seen in older infants receiving previous versions of the vaccine, the vaccine series (two or three doses, depending on the specific vaccine) should not be started after 15 weeks of age, and no dose should be given after 8 months of age.[1] Now, approximately 73% of U.S. infants receive a rotavirus vaccine, and the vaccine is credited with preventing about 50,000 hospitalizations for rotarvirus diarrhea in the United States each year.[1]

In the United States, for the past 25 years, the costs of routine childhood vaccines have been covered by the government for many children. The Vaccines for Children program accounts for half of all childhood vaccines in the United States and is credited with improving vaccination rates and reducing racial and ethnic disparities in vaccine coverage.[3] This government-funded program has sustainably overcome legislative, access, and financial barriers to childhood vaccination. Nonetheless, the administration of vaccines against all 16 diseases covered by this program is estimated to cost approximately $2,000 per child.[3] In India, rotavirus vaccine programs were instituted in 2016, with a phased approach including more states in each phase.[4]

Obviously, rotavirus vaccines are not just for Germany, the United States, and India. A recent review of the global impact of rotavirus vaccination evaluated pre-vaccine and post-vaccine data from 49 countries on six continents.[5] Overall, among preschool-age children, there was a 59% reduction in rotavirus-related hospitalization, a 36% reduction in acute gastroenteritis-related hospitalization, and a 36% reduction in gastroenteritis-related mortality.[5]

Worldwide, more than one-third of childhood deaths are associated with malnutrition. Acute gastroenteritis and recurrent bouts of diarrhea both are causes and consequences of malnutrition. In Kiribati, a Pacific island nation where malnutrition was common, the rate of gastroenteritis-related hospital admissions dropped by 44% with implementation of a rotavirus vaccination program, and the incidence of severe acute malnutrition dropped by 24%.[6]

Since rotavirus vaccines are live, there has been concern about giving them to hospitalized children who might inadvertently spread live vaccine virus to compromised patients. Thus, it has been routine not to give the vaccine to babies in neonatal intensive

care units until their day of discharge from the hospital, potentially limiting vaccine coverage in this vulnerable population. A recent review of 31 relevant papers shows that virus was shed by vaccinated children, but that transmission of infection was very rare and only occurred in household settings.[7] It was suggested that it might not be necessary to preclude hospitalized newborns from vaccination at the normal age-based schedule times.[7] ■

REFERENCES

1. Jacobson RM. Routine childhood vaccines given in the first 11 months of life. *Mayo Clin Proc* 2020;95:395-405.
2. Folorunso OS, Sebolai OM. Overview of the development, impacts, and challenges of live-attenuated oral rotavirus vaccines. *Vaccines* 2020;8:E341.
3. Schwartz JL, Colgrove J. The Vaccines for Children Program at 25 — access, affordability, and sustainability. *N Engl J Med* 2020;382: 2277-2279.
4. Malik A, Haldar P, Ray A, et al. Introducing rotavirus vaccine in the Universal Immunization Programme in India: From evidence to policy to implementation. *Vaccine* 2019;37:5817-5824.
5. Burnett E, Parashar UD, Tate JE. Global impact of rotavirus vaccination on diarrhea hospitalizations and deaths among children < 5 years old: 2006-2019. *J Infect Dis* 2020; in press. doi: 10.1093/infdis/jiaa081.
6. Lai J, Nguyen C, Babwaia B, et al. Temporal decline in diarrhea episodes and mortality in Kiribati children two years following rotavirus vaccine introduction, despite high malnutrition rates: A retrospective review. *BMC Infect Dis* 2020;20:207.
7. Sicard M, Bryant K, Muller ML, Quach C. Rotavirus vaccination in the neonatal intensive care units: Where are we? A rapid review of recent evidence. *Curr Opin Pediatr* 2020;32:167-191.

ABSTRACT & COMMENTARY

Immunomodulatory Treatment of Disseminated Coccidioidomycosis

By Dean L. Winslow, MD, FACP, FIDSA, FPIDS

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: A previously healthy 4-year-old boy with no prior serious illnesses was diagnosed with disseminated coccidioidomycosis with prominent skin and bone involvement. Despite treatment with liposomal amphotericin B, antifungal azoles, and surgical debridement, the patient developed progressive disease. Treatment with interferon-gamma slowed disease progression, and later treatment with interleukin-4 and interleukin-13 blockade induced remission of his infection.

SOURCE: Tsai M, Thauland TJ, Huang AY, et al. Disseminated coccidioidomycosis treated with interferon-γ and dupilumab. *N Engl J Med* 2020;382:2337-2343.

A previously healthy 4-year-old boy who lived in an area endemic for coccidioidomycosis presented with prominent skin and bone involvement due to disseminated coccidioidomycosis. The patient had clinical and serological evidence of disease progression despite treatment with liposomal amphotericin B, various azoles, and surgical debridement of bony lesions. The investigators carefully evaluated the child's immune system and found no clear genetic abnormalities to explain the child's severe, progressive disease.

Like most patients with disseminated coccidioidomycosis, the child exhibited no genomic evidence of any known, rare immune disease. However, comprehensive immunologic testing using functional assays showed exaggerated production of interleukin-4 and reduced production of interferon-gamma. Additional studies showed that in functional assays, it was demonstrated that the child's cells produced aberrantly high levels of the short, nonfunctional isoform of IL12RB1, leading to impaired interleukin-12 signaling and type 1 immunity. Treatment of the child with interferon-gamma appeared to slow, but not halt, disease progression. The addition of interleukin-4 and interleukin-13 blockade with dupilumab resulted in rapid resolution of the child's clinical symptoms.

■ COMMENTARY

I trained on the East Coast and in Louisiana, so I saw a lot of histoplasmosis and some blastomycosis. Then I practiced in Delaware during the first half of my career and saw only one case of coccidioidomycosis in a returning traveler during those years. When I returned to academic medicine in 2003 at our county hospital in San Jose, CA, (where Dr. David Stevens and his protégé, Dr. Larry Mirels, had established a center of excellence for the treatment of coccidioidomycosis years before), I had the privilege

of helping them care for many complicated and uncomplicated patients over the next 10 years. I quickly gained a lot of respect for this disease. Since I was trained in both adult and pediatric infectious disease, I attended regularly on the inpatient pediatric infectious disease consult service. I am still heartbroken when I remember the case of a beautiful 4-year-old boy from the San Francisco Bay Area who traveled to Phoenix for Christmas with his family and returned severely ill with disseminated coccidioidomycosis and central nervous system (CNS) involvement. The diagnosis was somewhat delayed but eventually was made at an outside hospital, and the patient was transferred to our hospital for higher-level care. Working with our pediatric colleagues, we treated him aggressively with liposomal amphotericin B, fluconazole, and even intrathecal amphotericin B. His course was complicated by stroke and significant hydrocephalus. I recommended a ventricular-peritoneal shunt be placed, and sadly, his surgery was complicated by perioperative cerebral hemorrhage, and he was placed on comfort care and died.

With my colleagues at Stanford, currently I am involved in the management of three adult patients with longstanding complicated CNS coccidioidomycosis. Although it has been known for some time that patients with disseminated coccidioidomycosis seem to have a disproportionate Th2 > Th1 response to *C. immitis*, the genetic basis for this still is not entirely clear in most patients. Dr. Steve Holland and his colleagues at the National Institute of Allergy and Infectious Diseases currently are conducting a large multicenter study collecting plasma and cells from patients with disseminated coccidioidomycosis to try to better characterize the subtle immune deficits these patients have to explain their susceptibility to disseminated disease. We have sent specimens on our patients to the National Institutes of Health, but no results have been published yet.

The use of interferon-gamma plus dupilumab dramatically helped the child described in this case report, but clearly larger studies with immunomodulators (tailored to the functional defects found in each patient) need to be performed since it is clear that this particular treatment will not necessarily help all patients with disseminated coccidioidomycosis. ■

ABSTRACT & COMMENTARY

A New Treatment for Recurrent Bacterial Vaginosis?

By Rebecca H. Allen, MD, MPH

Associate Professor, Department of Obstetrics and Gynecology, Warren Alpert Medical School, Brown University Women & Infants' Hospital, Providence, RI

Dr. Allen reports that she receives grant/research support from Bayer, and is a consultant for Bayer, Mylan, and Merck.

SYNOPSIS: In this randomized controlled trial of 228 women, *Lactobacillus crispatus* CTV-05 (Lactin-V) applied vaginally for 11 weeks reduced the incidence of recurrent bacterial vaginosis from 45% in the placebo arm to 30% in the Lactin-V arm.

SOURCE: Cohen CR, Wierzbicki MR, French AL, et al. Randomized trial of Lactin-V to prevent recurrence of bacterial vaginosis. *N Engl J Med* 2020;382:1906-1915.

Recurrent bacterial vaginosis (BV) is a problem that affects many women, with an estimated 50% of women developing a recurrence within 12 months of treatment.[1] The authors of this study tested the efficacy of a novel product, *Lactobacillus crispatus* CTV-05 (Lactin-V), in reducing bacterial vaginosis recurrence in this phase 2b clinical trial. This product contains a naturally occurring vaginal strain of *L. crispatus* in the form of a powder with 2×10^9 colony-forming units (CFU) preserved with inactive ingredients and administered via a vaginal applicator. Previously, the product was tested successfully in a phase 2a clinical trial.[2] This was a multicenter, randomized, placebo-controlled, double-blind trial to assess the efficacy of intravaginal Lactin-V in preventing a recurrence of BV among women who had received a diagnosis of BV at a screening visit. Women in the study were 18 to 45 years of age who met three of four Amsel criteria (thin, white, homogeneous discharge, > 20% clue cells on wet prep, vaginal pH of > 4.5, and positive whiff test), and were diagnosed with BV and treated with a five-day course of 0.75% metronidazole gel. A swab also was sent for a Gram stain to determine the Nugent

score (0-3, normal; 4-6, intermediate; and 7-10, indicative of BV).

Nonpregnant women whose Nugent score was 4 or greater and who had negative sexually transmitted infection (STI; HIV, syphilis, gonorrhea, chlamydia, and trichomonas) screening were seen within 48 hours of completing the vaginal metronidazole treatment. They were randomized in a 2:1 ratio to receive Lactin-V at 2×10^9 CFU per dose or matching placebo. The schedule consisted of four consecutive doses in week 1, followed by twice-weekly doses for 10 weeks. The patients were seen at four, eight, 12, and 24 weeks after treatment. The primary outcome was the percentage of participants who had recurrent BV, defined by three out of four Amsel criteria or a Nugent score of 4 or more at any follow-up visit up to and including week 12. Secondary outcomes included recurrent BV at 24 weeks and acceptability.

From April 2016 through February 2019, 228 women underwent randomization, 152 to the Lactin-V group and 76 to the placebo group. More than half the sample reported a history of five or more episodes of BV. Adherence to the treatment assigned was 77% in the Lactin-V arm and 74% in the placebo arm. In the intention to treat analysis, BV recurrence by week 12 occurred in 46 participants (30%) in the Lactin-V group and 34 participants (45%) in the placebo group (relative risk [RR], 0.66; 95% confidence interval [CI], 0.44-0.87). Among those without a known recurrence by week 12, an additional 13 (12%) participants in the Lactin-V group and seven (17%) in the placebo group had a recurrence by week 24 (RR, 0.73; 95% CI, 0.54-0.92). There was no difference between the two groups in terms of adverse events, both local (abnormal vaginal discharge, vaginal odor, genital itching) and systemic (abdominal pain, headache, frequent urination).

■ COMMENTARY

L. crispatus is a hydrogen peroxide-producing *Lactobacillus* that keeps the vaginal pH low and prevents other organisms from proliferating.[3] Lactobacilli predominate in healthy, normal vaginal flora, accounting for 70% to 90% of the microbiome. When this microbiome becomes disrupted, a biofilm infection, primarily consisting of *Gardnerella vaginalis*, adhering to the vaginal epithelium can occur. This biofilm promotes the growth of other anaerobic bacteria, leading to the symptoms of BV and malodorous vaginal discharge. The prevalence of BV varies by the population studied, but it can range from 15% to 40%.[3]

First-line treatment options include 0.75% metronidazole gel applied vaginally for five nights, clindamycin cream 2% applied vaginally for seven nights, or 500 mg of oral metronidazole taken twice a day for seven days. Recurrence rates are high, and the optimal strategy to manage recurrence is unknown. One common regimen to treat recurrence is 0.75% metronidazole gel applied twice weekly for four to six months after induction treatment.[4] However, more therapeutic options are needed, and I applaud the authors for taking on this issue. Despite BV's prevalence, it is not a well-funded disease.

The authors of this study showed a modest reduction in BV recurrence with the use of a novel product, Lactin-V, at 12 weeks and extending through week 24. The use of Lactin-V after treatment with 0.75% metronidazole gel is an attempt to repopulate the vagina with healthy lactobacilli. This makes biologic sense, more so than consuming probiotics orally, and the treatment was well tolerated. Presumably, the authors will continue to study this product in a phase 3 clinical trial and are aiming for U.S. Food and Drug Administration approval. For now, the product is not available commercially.

Nevertheless, besides the burden of BV on the individual patient, the disease is important because it increases the acquisition of other STIs and has been associated with an increased risk of preterm birth, endometritis after delivery or abortion, pelvic inflammatory disease, and infection after hysterectomy.[3] Although a 15% difference in recurrence rates is not drastic, women may be willing to use a vaginal product with minimal side effects to attempt to decrease their chance of recurrence. It is possible that different doses or lactobacilli products may have a different effect. It is hoped that exploration in this area will continue. ■

REFERENCES

1. Bradshaw CS, Morton AN, Hocking J, et al. High recurrence rates of bacterial vaginosis over the course of 12 months after oral metronidazole therapy and factors associated with recurrence. *J Infect Dis* 2006;193:1478-1486.
2. Hemmerling A, Harrison W, Schroeder A, et al. Phase 1 dose-ranging safety trial of *Lactobacillus crispatus* CTV-05 for the prevention of bacterial vaginosis. *Sex Transm Dis* 2009;36:564-569.
3. Paavonen J, Brunham RC. Bacterial vaginosis and desquamative inflammatory vaginitis. *N Engl J Med* 2018;379:2246-2254.
4. Workowski KA, Bolan GA, Centers for Disease Control and Prevention. Sexually Transmitted Diseases Treatment Guidelines, 2015. *MMWR Recomm Rep* 2015;64:1-137.

Updates

By Carol A. Kemper, MD, FACP

Metronidazole Neurotoxicity Is Real

SOURCE: Daneman N, Cheng Y, Gomes T, et al. Metronidazole-associated neurologic events: A nested-case control study. *Clin Infect Dis* 2020 Apr 18;ciaa395. [Online ahead of print].

For many years, in anecdotal reports and small series, metronidazole has been suspiciously related to the onset of encephalopathy, cerebellar findings with ataxia, tremor and nystagmus, and peripheral neuropathy — but this association has never been proven. The central nervous system findings were thought to be largely reversible and did not appear to be dose-related, whereas the peripheral nervous system findings appeared to be possibly dose- and duration-related.

To examine the effects of metronidazole nervous system toxicity, the authors performed a large-scale, population-based, nested case-control study of adults (≥ 66 years of age) living in Ontario, Canada. Cases were defined as those with cerebellar dysfunction, encephalopathy, or peripheral neuropathy within 100 days of receipt of either metronidazole or clindamycin (but not both), sometime between 2003 and 2017. Every case was matched by at least 10 patients without such symptoms, who also received metronidazole or clindamycin within the preceding 100 days and who served as controls. The average age of the cases was 78 years.

A total of 1,212 cases were identified and compared with 12,098 controls. Both central and peripheral nervous system adverse effects remained significantly more frequent in those receiving metronidazole, even when the analysis was adjusted for age, demographics, comorbidities, and other medications. The overall incidence of metronidazole neurotoxicity was 0.25%. Central neurologic complications were more than four times more likely than the occurrence of peripheral neuropathy. No dose response was observed. The mechanism behind these effects has not been defined.

Although this frequency of neurotoxicity may seem relatively small, metronidazole is used increasingly for many serious anaerobic infections in the hospital, as well as for outpatient infections, such as trichomonas and orodental infections. In the United States alone in 2017, more than 12,657,000 prescriptions were written for metronidazole. These data suggest that up to 2.5 million people were possibly at risk for CNS toxicity and another 625,000 for peripheral neuropathy from their drug exposure. This is definitely something to keep in mind when evaluating patients with neurologic complaints on metronidazole.

2020 Updated LTBI Treatment Guidelines

SOURCE: Sterling TR, Njie G, Zenner D, et al. Guidelines for the treatment of latent tuberculosis infection: Recommendations from the National Tuberculosis Controllers Association and CDC, 2020. *MMWR Recomm Rep* 2020;69:1-11.

I like to explain to patients (with drawings) the risk of progression of their latent tuberculosis infection (LTBI) to active tuberculosis (TB) is about 7% or one in 13 people. Line up 13 people with LTBI, and one of them will develop active TB. And, as you age, or if you develop diabetes or kidney disease, or need chemotherapy for any reason, that risk goes up to one in five. You get their attention, it sounds like you know what you are talking about, and it is especially effective if you add that they may be contagious and infect their kids or coworkers. Somehow if you say the risk is 5% to 10%, it does not sound as bad. Maybe people do not understand percentages. And what they really may not understand is that despite all of our modern care, the risk of mortality from active TB in the United States is a surprising 4% — worse than with COVID-19.

In the United States, 80% of active TB cases are due to progression of untreated LTBI. And at least 70% of active TB cases occur in foreign-born persons, many of whom do not want to believe they have been exposed to TB or understand the concept of latent TB. Capturing those individuals and treating them is important for controlling this infection in our communities.

The last official LTBI treatment guidelines were written in 2000. Since then, a nine-month course of isoniazid (INH) has been considered the standard of care for the treatment of LTBI in the United States, and was the comparator regimen for all others. New guidelines, published in February 2020, escaped most physicians' notice — coming just as COVID-19 hit. A committee formed by the Centers for Disease Control and Prevention (CDC) and the National Tuberculosis Controllers Association reviewed all

available publications and treatment data, focusing on 63 publications with meaningful data on LTBI treatment. They systematically graded the outcomes, including the benefits, hepatotoxicity, adverse effects, patient preference, regimen complexity, and cost, as well as the quality of the published data.

The committee simmered down their findings to recommend three rifamycin-based regimens and two alternate six- or nine-month isoniazid monotherapy regimens for LTBI treatment. They gave priority to shorter-course regimens with similar efficacy, higher rates of completion, and favorable tolerability compared with the former standard nine-month regimen of INH. Benefits and disadvantages presented are relative to this previous standard:

1. Three months of INH and rifapentine:
• Strongly recommended for adults and children > 2 years of age, including HIV-positive persons;
• Benefits: Equivalent effectiveness, less hepatotoxicity, shorter course, higher rates of completion when administered through directly observed therapy (DOT);
• Disadvantages: More adverse effects, higher cost, greater regimen complexity and higher pill burden, and lower rates of completion when not done through DOT.

2. Four months of rifampin:
• Strongly recommended for HIV-negative adults and children of all ages;
• Benefits: Similar effectiveness, less hepatotoxicity, fewer adverse effects, shorter course;
• Disadvantages: Numerous drug interactions; difficult to give in HIV infection; medication costs are higher (although offset by shorter course/fewer visits, may be more cost-effective on the whole).[1]

3. Three months of daily INH and rifampin:
• Conditionally recommended for adults and children of all ages, including HIV-positive persons when their regimen allows;
• Benefits: Similar effectiveness, lower risk of hepatotoxicity, and shorter course;
• Disadvantages: Higher rate of discontinuation for other adverse effects; risk for hepatotoxicity may be greater when both drugs given together; and numerous drug interactions.

4. Six months of INH:
• Strongly recommended for HIV-negative adults and children of all ages; conditionally recommended for HIV-positive adults and children;
• Benefits: Highly effective, but perhaps not quite as effective as nine or 12 months of INH (controlled data are lacking), inexpensive, shorter than nine months of INH;
• Disadvantages: Hepatotoxicity, longer treatment duration than the other proposed regimens, lower completion rates.

5. Nine months of INH:
• Conditionally recommended for adults and children of all ages, regardless of HIV status;
• Benefits: Highly effective, inexpensive;
• Disadvantages: Hepatotoxicity, longer treatment duration, lower completion rates.

It is important to keep in mind these guidelines are for patients with LTBI presumed sensitive to therapy. Recommendations for treatment of exposure to drug-resistant strains of TB were published separately in 2019. However, even in our northern California county, the risk of INH resistance among those with culture-positive TB with no prior history of TB who were born in the United States is 5%, and among those who are foreign-born it is 13%. INH resistance is highest in those born in Vietnam (18%), the Philippines (17%), and India (11%). Approximately 3% of all culture-positive TB cases in Santa Clara County were resistant to rifampin. Perhaps this is another reason to consider a rifamycin-based regimen. ■

REFERENCE

1. Bastos ML, Campbell JR, Oxlade O, et al. Health system costs of treating latent tuberculosis infection with four months of rifampin versus nine months of isoniazid in different settings. *Ann intern Med* 2020; June 16. doi: 10.7326/M19-3741 [Online ahead of print].

Risks of Hookah Smoking

SOURCE: International Society for Infectious Diseases. ProMED-Mail. Tuberculosis — Switzerland: Hookah usage. Dec. 27, 2019. www.promedmail.org

Smoking a hookah pipe is a centuries-old social custom in some societies. A pipe filled with "shisha" or flavored tobacco is passed around in a group, sometimes for hours, often at a hookah cafe. The same mouthpiece is shared, and the device may or may not be cleaned well between uses. Dried tobacco is combined with fruit pulp, molasses, and/or honey — or other flavorings like coconut, mint, or coffee. This lends a sweet quality to the smoke — which when drawn through a water bath gives the impression to many that smoking a hookah is safer than smoking cigarettes. Apparently, this is not the case: The tar from charcoal-burned tobacco in a hookah may be diminished by the water bath, but many of the cancer-causing chemicals, hydrocarbons, and metals found in today's tobacco are not filtered out by the water bath. But it is not just the chemicals: An average hookah contains as much tobacco as 20 filtered cigarettes.

The nicotine hit from a hookah is every bit as real — and as addictive — as smoking cigarettes. Further, the temperature of the smoke when heated electronically in newer hookahs, rather than by older charcoal versions, may be cidal to lung cells.

A recent University of California study found that one good draw on a hookah was similar to smoking one filtered cigarette, in terms of hazardous chemicals and metals. Further, the amount of carbon monoxide inhaled during one hookah session was similar to smoking 12 cigarettes.

Another adverse effect from sharing a hookah is the spread of oral and respiratory infections, such as herpes simplex, syphilis, and tuberculosis. While the water bath may filter out larger particles, it actually creates ultra-fine particles that can pass directly to the deeper parts of the lungs. Some extra-fine particles (< 0.1 micron) may pass directly through lung tissue into the bloodstream.

This Pro-MED-Mail report identified a 20-year-old man with cavitary tuberculosis (TB). He was a regular hookah smoker, and smoked at least five times per week with friends. The authors theorize that regular hookah smoking increased his risk for TB, with close, high-level contact, and spread of microparticles from the mouthpiece. Alternately, frequenting hookah cafés, crowded with people smoking and coughing, also could increase the risk for TB exposure. One wonders if the hot smoke may increase the risk of more severe bacterial or viral lung infection via repeated damage or inflammation to the tissues, similar to vaping. ■

CME QUESTIONS

1. Which of the following is true of routine rotavirus vaccination of infants?

a. It reduces rotavirus infection and rotavirus-related hospitalization.

b. It increases the risk of developing intussusception.

c. It is not practical in most countries of the world.

d. It should be delayed until the second half of the first year of life.

2. Which of the following is correct regarding the outbreak of COVID-19 in spring breakers in Cabo San Lucas?

a. Approximately one-fifth of those infected were asymptomatic.

b. Of those with symptoms and infected, all had fever.

c. Fifty percent of those who were infected required hospitalization.

d. The mortality rate in those who were infected was 17%.

3. Which of the following is correct regarding the infants < 90 days of age with SARS-CoV-2 infection described by Mithal and colleagues?

a. The mortality rate was 50%.

b. Most were severely hypoxic.

c. They had high viral loads.

d. None had a history suggestive of close contact with someone with COVID-19.

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.