

Infectious Disease [ALERT]

Incisive Commentary and Clinical Abstracts on Current Issues in Infectious Diseases

ABSTRACT & COMMENTARY

Is Sanitizer Better Than Soap?

By *Philip R. Fischer, MD, DTM&H*

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

SYNOPSIS: In day care settings, the implementation of hand hygiene programs reduced respiratory illness, absenteeism, and antibiotic use in children 0 to 3 years of age. Using hand sanitizer was more effective than washing with soap and water.

SOURCE: Azor-Martinez E, Yui-Hifume R, Munoz-Vico FJ, et al. Effectiveness of a hand hygiene program at child care centers: A cluster randomized trial. *Pediatrics* 2018;142:e20181245.

Respiratory tract infections are a major cause of illness, medical office visits, and antibiotic prescriptions for preschool-age children. Attendance at day care centers is a significant risk factor for becoming ill with respiratory tract infections, and children in day care have six to 10 respiratory tract infections each year. In school-age children, implementation of hand hygiene interventions reduces infections and school absenteeism. However, there are not many data about the effectiveness of hand hygiene programs in preschoolers in day care settings.

Thus, Azor-Martinez and colleagues randomized day care centers (and the children attending those

centers) to either hand hygiene (with groups randomized to use soap and water or hand sanitizer) or control groups. There were 25 state-registered day care centers in the area of a single city in Spain included in the study. Researchers included families of children 0 to 3 years of age who attended day care for at least 15 hours per week. Children with chronic illnesses and medication use that might alter the risk of respiratory tract infection were excluded.

Prior to the study period, parents and day care center staff who were randomized to an intervention group attended a one-hour workshop about hand hygiene. Participants were encouraged not to alter their usual post-toileting cleaning or the manner by

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Infectious Disease [ALERT]

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which they cleaned visibly dirty hands. However, they were instructed to use the intervention (soap-and-water washing or sanitizer use) before and after lunch, after outdoor play, prior to leaving school for home, after diapering, and after sneezing, coughing, or blowing their noses.

Sanitizer (70% alcohol) or soap (not specifically bactericidal) was provided for the schools and homes. Informational brochures about hand hygiene were available in the intervention day care centers. All day care centers, both in the intervention and control groups, provided informational sessions about respiratory infections and fever. Children were followed carefully for eight months.

The study included 960 children (82% of those who were eligible; the others did not have parental authorization for participation) from the 25 day care centers. One child in the sanitizer group had worsened atopic dermatitis; no other adverse effects were noted.

In this study, more than three-fourths of children received a 13-valent pneumococcal vaccine. Receipt of this bacterial vaccine did not significantly alter the risk of contracting a respiratory illness.

Overall, the 960 children had 5,211 respiratory illnesses during the eight-month study period. Children received antibiotics for 39% of those illnesses. The rate of respiratory infection was 21% lower in the sanitizer group than in the soap-and-water group, and 23% lower than in the control group. Day care absenteeism was significantly lower in the intervention groups (3.3% with sanitizer, 3.9% with soap and water) than in the control group (4.2%). The rate of antibiotic use was 31% lower in the sanitizer group than in the control group (which was similar to the soap-and-water group in terms of antibiotic use).

In summary, the Spanish team found that hand hygiene education and practice (whether with sanitizer or soap and water) reduced day care center absenteeism. Interestingly, children assigned to use sanitizer had significantly less infection, absenteeism, and antibiotic

use than those who used soap and water for hand hygiene.

■ COMMENTARY

What seems right is right — hand hygiene is effective in reducing illness and missed activity in preschool-age children. This is congruent with experience in older school-age children, but the availability of hand hygiene materials must be supplemented by instruction that promotes helpful behaviors.¹ Even though the impact of hand hygiene programs varies between settings,² many medical and education professionals are aware of the value of hand hygiene, and hand hygiene is increasingly implemented in many child care settings.

As we think back over the past two decades, we realize that hand hygiene in hospitals became a standard not just because of knowledge about the value of hand hygiene. Rather, people started cleaning their hands on entering and exiting hospital rooms when hand hygiene became easy and convenient. A systematic review suggests that multimodal strategies are needed to improve compliance with hand hygiene most effectively.^{3,4} Similarly, hand hygiene should become easy and convenient in day care centers and schools.

Why was sanitizing more effective than hand washing in this study? There are several potential explanations. First, sanitizer kills germs while soap and water “just” removes germs from hands. Future studies could compare the use of regular and bactericidal soaps in preventing infection in day care settings.

Second, the authors did not measure compliance with the implementation of sanitizing programs. It could be that hand washing was implemented less in the day care centers assigned to that intervention because it was not as easy or convenient. Hand washing requires sinks, a means of drying, and a longer pause at the sink. Sanitizing simply requires a quick hand motion while passing a dispenser and some hand rubbing while moving on toward the next activity. Whatever means of hand hygiene is suggested, success depends on effective implementation.

Third, the authors did not mention the means of drying in the soap and water group. Hand washing is most effective in reducing bacterial colonization when accompanied by the use of a sterile (rather than non-sterile) towel.⁵ If wet towels were reused repeatedly, the towels might have served as reservoirs of infection to facilitate ongoing microbial transmission.

Sanitizer use in hospitals might be facilitated by programs that have patients remind care providers to use sanitizer before and after patient contact.⁶ Similarly, parents and even children can be empowered to ensure that sanitizer is available conveniently in day care settings and for individual student use. By whatever means, hand hygiene can prevent illness in preschool-age children, decrease absence from planned activities, and reduce costs of medical care. It is time for implementation; faced with new data from Spain, don't just analyze, sanitize! ■

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ABSTRACT & COMMENTARY

Should Acute Appendicitis Be Managed Without Appendectomy?

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

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

SYNOPSIS: A retrospective cohort study that used national insurance claims data found patients with acute appendicitis who were treated nonsurgically had higher rates of complications and higher overall cost of care.

SOURCE: Sceats LA, Trickey AW, Morris AM, et al. Nonoperative management of uncomplicated appendicitis among privately insured patients. *JAMA Surg* 2018; doi: 10.1001/jamasurg.2018.4282. [Epub ahead of print].

The management of acute appendicitis without appendectomy has generated considerable interest among clinicians and patients in recent years. Several clinical trials have shown similar outcomes with appendectomy and nonsurgical management (i.e., antibiotics). However, deciding which patients should be managed without surgery has been challenging, and long-term data are scarce. Sceats and colleagues aimed to clarify these issues by comparing outcomes for patients with acute appendicitis who underwent appendectomy to those who received nonsurgical management.

The study was a retrospective cohort analysis that used information from a claims database of 40 to 50 million privately insured patients, mainly with

large employer-sponsored health plans. Researchers included patients who had an admission diagnosis of acute appendicitis between Jan. 1, 2008, and Dec. 31, 2014. Patients were divided into two groups: those who underwent appendectomy based on the presence of procedure codes and those who received nonsurgical management. The primary outcomes were rates of short-term (< 30 days) complications (i.e., emergency room visits, all-cause readmissions, appendicitis-associated readmissions, occurrence of abdominal abscess, and *Clostridium difficile* infection), and long-term (> 30 days) complications (i.e., readmission for small bowel obstruction, incisional hernia, and diagnosis of appendiceal cancer). The researchers conducted further post hoc analysis on the nonsurgical group to evaluate the rate

of management failure and the rate of appendicitis recurrence. Instead of using propensity score matching to balance the two groups, the authors used coarsened exact matching (CEM) because of a presumed bias in patients selected for nonsurgical management. This technique is based on forecasting after pruning observations such that the covariate distributions between the two groups are improved in the data that remain.

Researchers identified 58,329 patients with acute appendicitis during the study time period, of whom 55,709 (95.5%) underwent appendectomy and 2,620 (4.5%) received nonsurgical management. There were significant differences between the appendectomy and nonsurgical groups in terms of age (31.8 years vs. 34.2 years, respectively; $P < 0.001$) and the grouped Charlson comorbidity index ($P < 0.001$). Regarding short-term complications, patients who underwent nonsurgical management had significantly higher all-cause readmissions and appendicitis-associated readmissions ($P < 0.001$). Moreover, patients who had nonsurgical management were significantly more likely to develop an abdominal abscess than those who underwent appendectomy (2.3% vs. 1.3%, respectively; adjusted odds ratio [aOR], 1.42; 95% confidence interval [CI], 1.05-1.92). The results indicated no significant differences in the rates of emergency department (ED) visits or *C. difficile* infection.

Among long-term complications, those patients managed nonsurgically had higher rates of appendiceal cancer compared to those who underwent appendectomy (aOR, 4.07; 95% CI, 2.56-6.49). There were no significant differences in the rates of admission for small bowel obstruction or incisional hernias. The length of stay was slightly longer in the nonsurgical group (1.7 days vs. 1.6 days), and these patients also had more follow-up visits for appendicitis in the year following hospital discharge compared to those who underwent appendectomy (1.6 visits vs. 0.3 visits; $P < 0.001$). The nonsurgical group had a lower mean cost for the index hospitalization. However, when the total cost of care associated with appendicitis was evaluated, nonsurgical management was more expensive (\$14,934 vs. \$14,186). The overall failure rate of nonsurgical management was 3.9% (101 of 2,620 patients), and the median time from the initial diagnosis to management failure or recurrence was 42 days (range, 8-125 days).

■ COMMENTARY

This is an interesting and important study because it informs clinicians about managing acute appendicitis nonsurgically in a real-world setting, i.e., outside

of a clinical trial. Of the 4.5% of patients managed nonsurgically, only 3.9% required an appendectomy during a mean follow up of 3.2 years. This is in contrast with results from randomized clinical trials, which had rates of approximately 27%. The reason for this discrepancy is uncertain and might be a result of the patient populations studied, although an alternative explanation is that patients in clinical trials are monitored more carefully. The operative group had lower rates of readmissions, office visits, and complications, including abscess formation and appendiceal cancer. Indeed, a recent randomized clinical trial found a high rate of appendiceal cancer in patients treated nonsurgically for peri-appendicular abscess.¹

Although the cost of the initial hospitalization for acute appendicitis was lower in the nonsurgical group, this benefit was more than offset by the costs that came afterward, including more office and ED visits. The higher rates of complications also led directly to increased costs, which were 5.5% greater in the nonsurgical group. Moreover, the time out of work that the nonsurgical patients experienced because of their additional visits was an indirect cost that was not factored into the economic analysis.

There were a few limitations to the study. First, the cohorts were significantly different in terms of age and Charlson comorbidity index. Second, the retrospective design makes the presence of unmeasured confounding variables a possibility. Third, there also may have been selection bias in favor of nonsurgical management because this approach often is used when patients are deemed poor surgical candidates. The authors attempted to account for this possibility using the CEM algorithm and multivariate analysis.

Many, if not most, patients would choose to avoid appendectomy if they were told there was a reasonable chance of cure by nonsurgical management. It does them a disservice if the best available evidence suggests otherwise. Thus, the study by Sceats and colleagues should be taken into account by clinicians (both surgeons and non-surgeons) during conversations with patients who have acute appendicitis about their expectations and possible outcomes. ■

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ABSTRACT & COMMENTARY

The Longhorned Tick: Is It Coming to a Place Near You?

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 tick that can transmit several infections has been newly identified in the United States.

SOURCE: Beard CB, Occi J, Bonilla DL, et al. Multistate infestation with the exotic disease-vector tick *Haemaphysalis longicornis* — United States, August 2017–September 2018. *MMWR Morb Mortal Wkly Rep* 2018;67:1310-1313.

In August 2017, a sheep in New Jersey was found to be infected with *Haemaphysalis longicornis* (see Figure 1), the first time that tick had been found in the United States. This raised concern because the tick is known to be the vector of several infectious diseases.

Through September 2018, CDC has accumulated 53 reports of identification of this tick, variously known as the longhorned tick, the Asian tick, and the cattle tick, recovered from domestic animals, wildlife, and vegetation, as well as from two humans. The tick was detected from eight eastern states and from Arkansas. (See Figure 2.)

Neither the ticks nor their hosts were screened for the presence of pathogens, but no cases of illness in hosts were reported. Examination of historical archived samples demonstrated that the tick had been present in the United States for years prior to August 2017, with, e.g., its identification in samples collected from

a deer in West Virginia in 2010 and a dog in New Jersey in 2013.

■ COMMENTARY

H. longicornis is native to eastern China, the far east of Russia, Japan, and Korea, and it is also found, as the result of later introductions, in New Zealand, Australia, and some western Pacific island nations. In each of these places, it is an important vector of human and animal disease. The tick is known to transmit the agent of severe fever with thrombocytopenia syndrome (SFTV virus) and Japanese spotted fever (*Rickettsia japonica*). Pathogens identified in the tick include ones causing infections in the United States: *Anaplasma*, *Borrelia*, and *Ehrlichia*. The tick also may be a vector of Powassan and

Figure 1: Longhorned Tick



Source: Centers for Disease Control and Prevention. What you need to know about Asian longhorned ticks — A new tick in the United States. Available at: <https://www.cdc.gov/ticks/longhorned-tick/index.html>. Accessed Dec. 7, 2018.

Figure 2: Counties and County Equivalents* Where *Haemaphysalis longicornis* Has Been Reported (N = 45) — United States, August 2017 - September 2018



Source: Beard CB, Occi J, Bonilla DL, et al. Multistate infestation with the exotic disease-vector tick *Haemaphysalis longicornis* — United States, August 2017–September 2018. *MMWR Morb Mortal Wkly Rep* 2018;67:1310-1313.

Heartland viruses, as well as *Theileria*, a parasite that infects ruminants. *H. longicornis* infestation of dairy cattle in Australia and New Zealand is associated with a marked reduction in milk production.

It is unlikely that *H. longicornis* is restricted to the nine states in which it has been found to date. It is

very likely that the tick will prove to be a vector of one or more infectious diseases in the United States.

The CDC is working to define its epidemiology further and its potential for pathogen transmission to humans, cattle, and other animals. ■

ABSTRACT & COMMENTARY

Preventing *Clostridioides difficile* Infections: Early De-escalation of Antipseudomonal Antibiotics

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: Early discontinuation of empirically administered antipseudomonal antibiotics may prevent many cases of *Clostridioides difficile* infection.

SOURCE: Seddon MM, Bookstaver PB, Justo JA, et al. Role of early de-escalation of antimicrobial therapy on risk of *Clostridioides difficile* infection following *Enterobacteriaceae* bloodstream infections. *Clin Infect Dis* 2018; doi: 10.1093/cid/ciy863. [Epub ahead of print].

Seddon and colleagues performed a retrospective cohort study to examine whether early (within 48 hours) de-escalation of empiric antimicrobial therapy in adult patients with monomicrobial bloodstream infection (BSI) due to *Enterobacteriales* was associated with a reduced incidence of *Clostridioides difficile* infection (CDI). In the study, 414 patients received empiric antibiotics for > 48 hours, while 394 patients received them for < 48 hours. The most frequently isolated organisms were *Escherichia coli* (56%) and *Klebsiella* spp. (21%). The most frequently identified primary sources of bacteremia were the urinary tract (56%) and the abdominal cavity (13%).

Twenty-nine patients developed CDI diagnosed by polymerase chain reaction (PCR) within 90 days of their BSI. After eliminating from consideration patients with incomplete follow-up, the overall incidence of CDI was 4.4%, and 24 of 29 patients had onset during the index hospitalization. CDI occurred 4-27 days (median, 11 days) after BSI.

The incidence of CDI was 7.0% (95% confidence interval [CI], 4.2-9.8%) in those who received empiric antipseudomonal antibiotics for > 48 hours and only 1.8% (95% CI, 0.4-3.2%; log-rank, $P = 0.002$) in those who received it for < 48 hours.

After propensity adjustment, receipt of antibiotics with antipseudomonal activity for > 48 hours, CDI (HR, 3.38 [95% CI, 1.40-9.47; $P = 0.006$]), and the presence of end stage renal disease (HR, 4.04 [95% CI, 1.75-8.78; $P = 0.002$]) were independent risk factors for the development of CDI. A further analysis censored eight (28%) patients in the CDI group because they were inappropriately tested and may have been carriers, but this did not significantly affect the results above.

■ COMMENTARY

In a retrospective analysis of 37,000 hospitalized patients, receipt of vancomycin, cefepime, piperacillin-tazobactam, or a carbapenem — the last three of which have antipseudomonal activity — were identified as risk factors for the development of CDI.¹ This study by Seddon and colleagues provides further evidence that antipseudomonal antibiotics may create a higher risk of CDI development than others that lack that activity, but the reason for this is unclear. It should be noted, e.g., that carbapenems and piperacillin-tazobactam have significant anti-anaerobe activity, a factor that likely is a contributing feature.

Antipseudomonal antibiotics are frequently included in empiric regimens, most often needlessly. The

key lesson from this study is that when they are administered for this purpose, these drugs should be discontinued as early as possible, preferably within 48 hours of initiation. ■

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ABSTRACT & COMMENTARY

Acute Flaccid Myelitis 2018

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: The number of reported cases of acute flaccid myelitis, a paralytic disease of unknown etiology, has increased.

SOURCE: McKay SL, Lee AD, Lopez AS, et al. Increase in acute flaccid myelitis — United States, 2018. *MMWR Morb Mortal Wkly Rep* 2018;67:1273-1275.

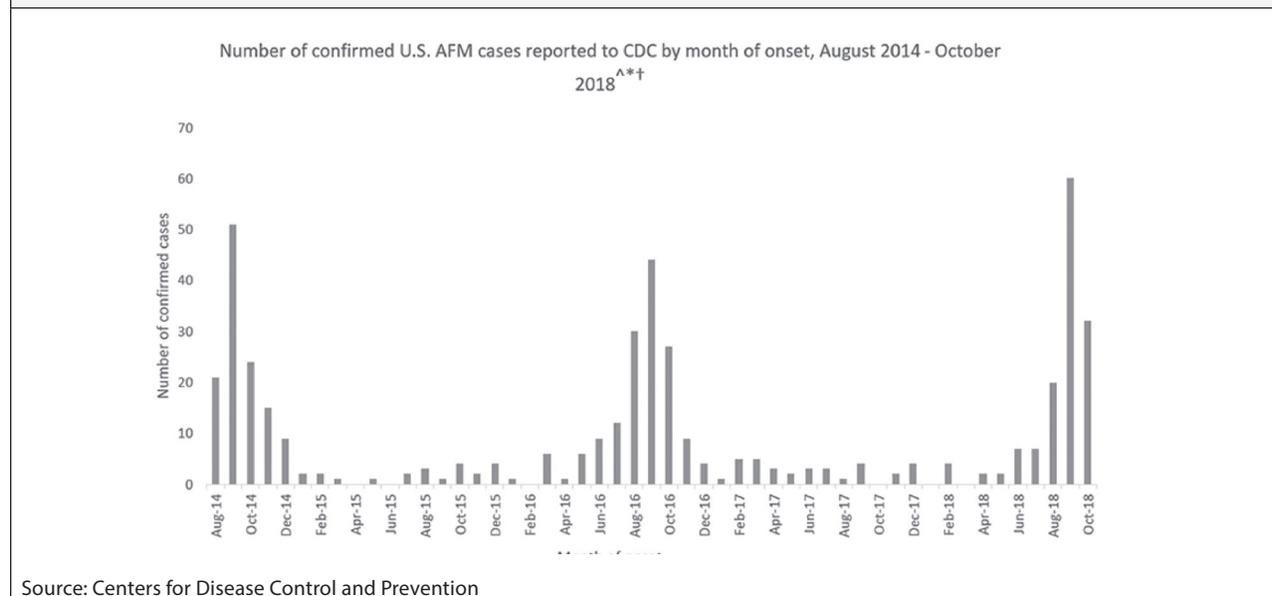
The Centers for Disease Control and Prevention (CDC) recognized an apparent increase in reported cases of acute flaccid myelitis (AFM) when 120 cases were confirmed in the summer and autumn of 2014. This led to the establishment of standardized surveillance the following year. (See Figure 1.) Although only 21 confirmed cases and three probable cases were identified in 2015, cases have rebounded subsequently. From Jan. 1 to Nov. 2, 2018, there was a threefold increase over the same period in 2017. Among the 106 reported cases that had undergone classification (see Table 1), 80 were confirmed, six were probable, and the diagnosis was rejected in 20. The patients' ages ranged from 7 months to 32 years,

with a median of 4 years and interquartile range of 2.4-7.6 years; 59% were male.

Signs and/or symptoms suggesting the presence of a viral illness had occurred in the four weeks prior to the onset of limb weakness in 79 (99%) patients. Thirty-eight (47.5%) patients had only upper limb weakness, seven (8.8%) had only lower limb involvement, 12 (15.0%) had weakness in two to three limbs, and 23 (28.8%) had involvement of all four limbs.

The results of cerebrospinal fluid (CSF) tests were available for 78 (98%) patients. Pleocytosis was

Figure 1: Confirmed Acute Flaccid Myelitis Cases Reported to CDC



Source: Centers for Disease Control and Prevention

Table 1: Acute Flaccid Myelitis Clinical Criteria

Clinical Criteria

An illness with onset of acute flaccid limb weakness

Laboratory Criteria

- Confirmatory Laboratory Evidence: a magnetic resonance image (MRI) showing spinal cord lesion largely restricted to gray matter[†] and spanning one or more vertebral segments
- Supportive Laboratory Evidence: cerebrospinal fluid (CSF) with pleocytosis (white blood cell count > 5 cells/mm³)

Case Classification

Confirmed:

- Clinically compatible case AND
- Confirmatory laboratory evidence: MRI showing spinal cord lesion largely restricted to gray matter[†] and spanning one or more spinal segments

Probable:

- Clinically compatible case AND
- Supportive laboratory evidence: CSF showing pleocytosis (white blood cell count > 5 cells/mm³)

* Spinal cord lesions may not be present on initial MRI; a negative or normal MRI performed within the first 72 hours after onset of limb weakness does not rule out AFM.

† Terms in the spinal cord MRI report such as “affecting mostly gray matter,” “affecting the anterior horn or anterior horn cells,” “affecting the central cord,” “anterior myelitis,” or “poliomyelitis” would all be consistent with this terminology.

Source: Centers for Disease Control and Prevention. Available at: <https://wwwn.cdc.gov/nndss/conditions/acute-flaccid-myelitis/case-definition/2018/>. Accessed Dec. 9, 2018.

present in 65 (83%), with 6-814 nucleated cells per mm³ (median 103/mm³), with most having lymphocyte predominance. The median protein and glucose concentrations were 47 mg/dL (range, 8-289) and 59 mg/dL (range, 40-138).

Polymerase chain reaction (PCR) testing of CSF, upper respiratory samples, and/or stool/rectal swabs detected enterovirus/rhinovirus (EV/RV) in 38 (54%)

patients, with identification of EV-A71 in 11 (29%), EV-D68 in 14 (37%), and other viruses in 13 (34%). Only two patients had positive CSF samples — EV-A71 and EV-D68 in one each.

■ **COMMENTARY**

AFM is a subtype of acute flaccid paralysis, which also includes a variety of paralytic diseases such as Guillain-Barré syndrome, acute transverse myelitis, and other entities.

The etiology of most cases of AFM remains unknown. A chief suspect has been EV-D68, an outbreak of which in 2014 was associated temporally with the emergence of AFM that year. However, EV-D68 was detected in the CSF of only two patients in the interval examined by McKay and colleagues, although it was found in other samples in several patients. The inability to detect a virus in CSF at the time of paralysis in most cases, together with the fact that 99% of patients had a preceding illness consistent with a viral infection, suggests the possibility that AMF may represent a post-infectious immunological disease.

CDC recommends the following:

“Parents and caregivers are urged to seek immediate medical care for a child who develops sudden weakness of the arms or legs. In the evaluation of a child with acute flaccid limb weakness, clinicians are advised to inquire about recent fever with or without antecedent respiratory or gastrointestinal symptoms and to collect timely specimens for viral testing, including CSF, serum, respiratory, and stool specimens. Additional information for clinicians is available at <https://www.cdc.gov/acute-flaccid-myelitis/hcp/index.html>. Patients with acute flaccid limb weakness should be reported to their health departments as soon as possible regardless of laboratory or MRI findings.” ■

ABSTRACT & COMMENTARY

Antibiotic Decision-Making Between Medical and Surgical Teams

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

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

SYNOPSIS: In an observational study conducted at an academic medical center in London, researchers looked at factors involved in decision-making. The presumptive diagnosis of infection by the emergency department (ED) influenced decision-making by both medical and surgical admitting teams. Medical teams tended to use a multidisciplinary approach to antibiotic decision-making. Surgical teams often delegated antibiotic decision-making to the most junior members of the surgical team.

SOURCE: Charani E, Ahmad R, Rawson TM, et al. The differences in antibiotic decision-making between acute surgical and acute medical teams: An ethnographic study of culture and team dynamics. *Clin Infect Dis* 2018; doi: 10.1093/cid/ciy844. [Epub ahead of print].

This observational study was conducted in London at an academic medical center, and it incorporated more than 500 hours of observation over a two-year period. The researchers examined cultural determinants of antibiotic decision-making among acute medical teams and surgical teams. In medicine, the decision-making process could be characterized as collectivist (using input from pharmacists, infectious disease specialists, and medical microbiology teams), informed by policy, and with an emphasis on de-escalation of therapy. The investigators noted that among acute medicine teams, gaps in antibiotic decision-making mainly occur during the transition between the emergency department and inpatient teams. In these transitions, the ownership of the antibiotic prescription can become lost.

For the surgery teams, the priorities are divided among the operating room, outpatient clinic, and ward settings. In the ward, senior surgeons are absent frequently, and complex medical decisions often are left to junior staff. The result is defensive decision-making, which leads to antibiotic use that is prolonged and inappropriate. In medicine, the initial diagnosis of infection made in the emergency department influenced subsequent prescription of antibiotics. In the surgery setting, decision-making about antibiotics is thought of as a nonsurgical intervention that house staff or other specialties can manage.

■ COMMENTARY

This study really resonated with me and reinforced many of my pet peeves about antibiotic overprescribing in 21st century medicine in the

United States. I was heartened that our British internal medicine colleagues seem to rely on “collectivist” decision-making to prescribe antibiotics more than we do in the United States. Although it is true in the United States that surgical specialists often delegate antibiotic prescription to the more junior members of the team, I am not sure that they perform that much worse than our medicine teams do.

I have become increasingly convinced that much of the over-prescription of antibiotics by many doctors in the United States actually is driven by fear. Although guidelines such as the Surviving Sepsis Campaign guidelines have increased awareness of early recognition and appropriate treatment of sepsis, I am concerned that the application of these guidelines in the absence of discernment has resulted in “fear-based” over-prescription of broad-spectrum antibiotics. (One example I give is the common setting of a hospitalized patient who develops massive hemorrhage, is noted incidentally to have leukocytosis, and then reflexively is given vancomycin plus meropenem since they “don’t want to miss sepsis.”)

I hope that over the next few months the concerns of many infectious disease specialists will be recognized and we can work with our critical care medicine colleagues to develop truly evidence-based guidelines for the management of sepsis.¹ ■

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Circulation of a Novel Vaccinia Virus in Brazilian Equids

SOURCE: Borges IA, Reynolds MG, McCollum AM, et al. Serological evidence of *Orthopoxvirus* circulation among equids, southeast Brazil. *Front Microbiol* 2018;9:402.

The origin of vaccinia virus (VACV), used for vaccination against smallpox, has long been debated, although for years the virus has been recognized as not being specifically a cowpox virus of lore. Complicating matters, 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 VACV. In a 2017 *New England Journal of Medicine* publication, which was reviewed in *Infectious Disease Alert* one year ago, researchers observed that a recently discovered sample of 1902 smallpox vaccine, manufactured by an American company in Philadelphia, most closely resembled natural horsepox virus and not cowpox virus.¹ DNA extracted from that vaccine was submitted to whole genome amplification and compared with 65 other published genome *Orthopoxvirus* sequences. The 1902 VACV strain most closely resembled horsepox virus (99.7%), using different phylogenetic algorithms, although 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.

Formerly, Orthopox viruses were classified on the basis of morphology and the affected animal species. The genus includes vaccinia, variola, cowpox, horsepox, buffalopox, camelpox, catpox, elephantpox, rabbitpox, monkeypox, alastrim, and ectromelia (mousepox), and has been delineated by genomics. In reality, these viruses may cross-infect different animal species, with varying disease severity, and all of these strains are genetically similar. Horsepox virus reportedly no longer exists in nature, although scientists in the United States published the sequence of horsepox virus in 2006, derived from a wild strain recovered 40 years earlier from horses in Mongolia.

Following the WHO's campaign to eradicate smallpox (1966-1980), VACV emerged as a zoonosis in India, Pakistan, and Brazil, mostly in dairy cattle. Outbreaks of VACV were reported in 1999 in Brazil, affecting both dairy cattle and the humans who

milked them. Since then, it has become largely an occupational disease of milkers, and is referred to as "bovine vaccinia." Subsequently, an outbreak of vaccinia occurred in a horse-breeding facility in 2008 — and further outbreaks were reported in equids in Brazil in 2011 and 2014. However, none of these outbreaks in equids seemed to affect humans.

Borges and colleagues performed a serologic survey of 621 equids in Brazil, including 478 randomly selected horse samples collected and banked for various purposes since 2003, 74 sera from the outbreak in 2011, and 69 other randomly selected serologic equid samples. Remarkably, 128 (20.6%) of the samples were seropositive for antibody to "*Orthopoxvirus*" by either ELISA or PRNT. According to the owners, none of these horses had shown clinical evidence of vaccinia. Samples collected as early as 2003-2004 were positive — even before the recognized outbreak in 2008. Seropositivity varied by region (from 4.8% to 29.4%), and clustering in certain farms and areas was evident.

Since no *Orthopoxvirus* other than VACV has been found in circulation in Brazil, the authors presumed their serologic data was evidence of long-standing circulation of VACV in horses and donkeys in their country. In more recent years, equid cases of vaccinia have been reported in the neighboring South American countries Uruguay, Argentina, and Columbia. However, this virus has not yet been sequenced, and it remains a mystery why this strain of "vaccinia pox" has not caused clinical disease in humans. This low-level virus, whatever it is, in fact may be unrelated to the WHO smallpox campaign in 1966-1980. Since many countries used horses for replication of VACV for human use for decades, it is conceivable equids have evolved their own strain of vaccinia pox, derived from one of those original horse-derived vaccine strains.

REFERENCE

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.

Chopin's Brandied Heart

SOURCE: Witt M, Szklener A, Marchwica W, Dobosz. Disease not genetic but infectious: Multiple tuberculomas and fibrinous pericarditis as symptoms pathognomonic for tuberculosis of Frederic Chopin. *J Appl Genet* 2018;59:471-473.

It is a macabre tale: Many believe that Frederic Chopin, the great Polish pianist and composer, died from progressive tuberculosis in Paris in 1849. However, the exact cause of his death is not known. He had been exiled from his beloved home country for years, and, on his deathbed, he allegedly whispered to his sister, Ludwika, that he wished for his heart to rest in Poland. And so, while his body was buried in France, she smuggled his heart in a glass jar, past border guards, to her home in Warsaw. The heart ostensibly was preserved in cognac or brandy, since that was the only alcohol of sufficient strength at the time. The heart then passed through the hands of various relatives before it was enshrined in a pillar at Holy Cross Church in Warsaw. It briefly fell into the hands of Nazis during World War II, but then was returned to Holy Cross Church on Oct. 17, 1945, on the 96th anniversary of Chopin's death. For years, relatives consistently declined requests to analyze the jar's contents.

However, in April 2014, the family allowed access to the specimen — only because of concerns about the amount of liquid preservative remaining in the jar. In the dark of night, completely in secret, the heart was removed from its hiding place for inspection. Only 13 individuals were present, including one forensic scientist and the Archbishop, who stood by, praying. Only nondestructive specimens were going to be allowed, such as samples of the liquid for genetics. The heart appeared to be in excellent condition, floating within an amber liquid — and remained fully submerged. So, in the end, only a superficial inspection and about 1,000 photos were allowed before the jar was sealed with beeswax and replaced within its crypt. The secret investigation was not revealed for another five months.

Dr. Tadeusz Dobosz, the forensic scientist on the team, was allowed to visually inspect the heart within the jar (photos are available on the internet), and described a generally enlarged heart, completely coated with a thickened white “tapestry” of fibrous tissue, and studded with shiny white pearls of glossy tissue. These are believed to be consistent with tuberculomas, and the white coating consistent with a diffuse, organizing inflammatory process, or

what is referred to in the pathological literature as a “frosted heart.” The heart also had areas of nodular hyalinization and “organizing serosanguineous effusions” consistent with granulomatous caseation, predominantly involving the right side of the heart. All of this is very different from the post-mortem crystalline precipitates that can be seen in other types of preserved specimens. Dr. Dobosz believes the appearance of the heart is consistent with a diagnosis of tuberculous pericarditis, which likely contributed to more rapid downhill course at the end of Chopin's chronic illness.

The Scent of Malaria

SOURCE: Lindsay S, Pinder M, Squires C, et al. Can medical-detection dogs identify people with malaria parasites? Abstract #32. American Society for Tropical Medicine and Hygiene Annual Meeting; New Orleans: Oct. 29, 2018.

Quick and easy, noninvasive diagnostic tools are always welcome, especially in poor and rural areas. These researchers had the ingenious idea that if scent dogs can be trained to detect drugs, cheese, fruit, and vegetables at ports of entry, could they be trained to detect the odor of malaria infection? Researchers obtained blood samples from 600 children ages 5 to 13 years in the upper river region of Gambia in West Africa and assessed for malaria. The children then received socks to take home and wear in bed at night. A total of 175 socks were collected, including socks from 30 children with positive blood smears and 145 without malaria. The socks were frozen and shipped to England. After four months of training, two dogs (a Labrador and a Labrador-golden retriever cross) performed a “blinded” study. The dogs correctly identified 70% of socks from children with malaria, and 90% of socks from children without the disease.

The use of scent dogs could prove of tremendous benefit in the more rapid identification of individuals carrying malaria, since generally only those people with symptoms are screened. The alternative is to screen everyone in a community with blood smears, which simply is not practical. The real question is, how much better would the dogs perform in real time if the socks weren't frozen? ■

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CME QUESTIONS

1. Which of the following is true of the use of hand sanitizer in day care settings?
 - a. It reduces the rate of respiratory illness.
 - b. It decreases absenteeism.
 - c. It is associated with less antibiotic use.
 - d. All of the above are true.
2. Which of the following is correct regarding the longhorned tick, *Haemaphysalis longicornis*?
 - a. It is known to be native to Africa.
 - b. It is known to transmit *Borrelia burgdorferi*, the agent of Lyme disease, in the United States.
 - c. It is known to transmit a rickettsial infection (Japanese spotted fever) in Japan.
 - d. It has been identified in the United States as far west as Colorado.
3. Which of the following is correct regarding de-escalation of antibiotic therapy in patients with monomicrobial bacteremia due to *Enterobacteriales*?
 - a. De-escalation of empiric ceftriaxone is associated with a significantly reduced incidence of in *Clostridioides difficile* infection.
 - b. De-escalation of empiric ciprofloxacin is associated with a significantly reduced incidence of *Clostridioides difficile* infection.
 - c. De-escalation of empiric gentamicin is associated with a significantly reduced incidence of *Clostridioides difficile* infection.
 - d. De-escalation of empiric antipseudomonal beta-lactam antibiotics is associated with a significantly reduced incidence of *Clostridioides difficile* infection.
4. Which of the following is correct regarding acute flaccid myelitis (AFM)?
 - a. AFM has been demonstrated to be due to enterovirus D68.
 - b. Almost all patients reported symptoms/signs consistent with a viral illness in the four weeks preceding the onset of limb weakness.
 - c. Cerebrospinal fluid pleocytosis is absent in the majority of cases.
 - d. AFM disproportionately affects adults.

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.