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Infectious Disease [ALERT]

Incisive Commentary and Clinical Abstracts on Current Issues in Infectious Diseases

ABSTRACT & COMMENTARY

Antibiotic Use in Infancy Associated With Allergic Disease During Childhood

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 a large population-based study, antibiotic use during the first six months of life was associated with a two-fold increase in asthma and a 1.5-fold increase in allergic disease during early childhood.

SOURCE: Mitre E, Susi A, Kropp LE, et al. Association between use of acid-suppressive medications and antibiotics during infancy and allergic diseases in early childhood. *JAMA Pediatrics* 2018;172:e180315.

Aware that allergic diseases are prevalent in pediatric patients and concerned that alterations in the microbiome might predispose patients to develop allergies, a group of U.S. military researchers retrospectively reviewed charts of 792,130 children who were covered by Department of Defense insurance. Subjects of the study had to enter the insurance-supported system by 35 days of age and continue through at least the first year of life. Those who spent more than a week in the hospital right after delivery and those who were diagnosed with allergy during the first six months of life were excluded from the study. The study subjects were born from 2001 to 2013.

Researchers noted whether the participants had received an antibiotic during the first six months of life. A positive "outcome" included children who, after the first six months of life, developed any allergy, including anaphylaxis, urticaria, asthma, food or medication allergy, allergic rhinitis or conjunctivitis, or atopic or contact dermatitis. Follow-up data were available on included children for a median of 4.6 years.

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Infectious Disease [ALERT]

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

Overall, 17% of children were prescribed an antibiotic during the first six months of life. The risk of being diagnosed with an allergy increased with antibiotic exposure. Based on adjusted hazard ratios, the risk of developing asthma increased 2.09-fold with antibiotic exposure. Similarly, the risk increased 1.75-fold for allergic rhinitis, 1.51-fold for anaphylaxis, and 1.42-fold for allergic conjunctivitis. The risk of developing food allergy was 1.14-fold higher with antibiotic exposure; this included increased risks of milk and egg allergy but no increased risk of peanut and seafood allergy. The risk did not differ based on whether the children received a full 10-day course of antibiotics or a prescription for a shorter duration.

The authors pointed out that their findings were consistent with a 2011 systematic review linking infant antibiotic use to a 1.52-fold higher risk of developing allergies as well as a 2017 paper demonstrating that antibiotic use in the first three months of life was associated with increased risk of both food and non-food allergies.

Mitre and colleagues advanced the notion of altered microbiomes due to antibiotic use as a plausible explanation for the link between early antibiotic use and the subsequent development of allergic disorder, presumably because of the gut flora's influence on T cell regulation. This is not merely a human phenomenon. These investigators cited mouse studies showing that early life antibiotic exposure in those rodents also increased the risk of developing allergies later.

Incidentally, this study included a concurrent evaluation of the risk of antacid use during infancy on the subsequent development of allergic disease. As with antibiotic use, the use of antacids during the first six months of life was associated with an increased risk of developing allergic disease later — 1.25-2.59-fold risk for developing various allergies following the early life use of either an H2 blocker or a proton pump inhibitor.

■ COMMENTARY

The new availability of antibiotic therapy during the last century was credited with saving the life of pneumonia-stricken Winston Churchill. Of course, millions of people since then also have been affected, often favorably, by antibiotic use. Antibiotics can be powerful medications, but they also carry significant risk.

[Despite the proven effectiveness of antibiotics in treating infections, there are widespread risks to antimicrobial therapy.]

Antibiotic use is common, even during the first six months of life. In the population of U.S. military dependents studied by Mitre and colleagues, 17% of children received at least one course of antibiotics. Antibiotic use also is common in other parts of the world. In several cities in Asia, Africa, and South America, the majority of children receive antibiotics during the first six months of life.[1] In Europe, antibiotics are used less, and use varies in different countries; upper respiratory tract infections are treated with antibiotics 19% of the time in Italy but only 1% of the time in Switzerland, and otitis media prompts antibiotic use 82% of the time in Italy but just 55% of the time in the Netherlands.[2] Overall, antibiotics are given 0.2 to 1.3 times per child during the first year of life in various European countries.[2]

Despite the proven effectiveness of antibiotics in treating infections, there are widespread risks to antimicrobial therapy. Childhood obesity is more common in children who received antibiotics during infancy, and using antibiotics during the first six months of life increases the risk of overweight and obesity 1.2-fold.[3,4] Now, we have further evidence linking early antibiotic use and the subsequent development of asthma and allergies. In fact, early antibiotic use might be blamed for doubling the incidence of asthma and increasing obesity by 20%; these risks seem subtle, as they are dispersed through the population, but they could have mushroom cloud-type devastating consequences on the current generation of growing children. However, these new data should be considered carefully before blaming antibiotics for too many of our problems.

The obvious conclusion is that antibiotics alter the pediatric patient in ways that make future development of allergies more likely. Mitre and colleagues postulated that the mechanism of the association might be through alterations in the microbiome. Clearly, antibiotic use alters intestinal flora, and allergic disease has been associated with alterations in the microbiome. The authors further speculated that antacids increase the risk of allergic disease through intestinal fluid pH changes that also alter intestinal flora.

Is the obvious conclusion correct? The authors wisely noted that some of the antibiotics might have been given to children whose symptoms actually were from allergies even though the allergic disease had not yet been diagnosed. However, there could be other explanations. Even if allergic disease varies with changes in the microbiome, it could be that there were other reasons for alterations in intestinal flora. The study was conducted in a military population, and military children potentially are subject to frequent geographical displacement. International travel exposes children to varied germs and changes their microbiomes. Perhaps it was travel that prompted altered microbiota (and subsequent allergies) rather than the antibiotic. And, perhaps it was the travel that provoked fussiness that was interpreted as a need for antibiotic or antacid treatment. Of course, this is speculative, but further studies will be needed to determine if the association of antibiotic use with subsequent allergic disease holds true when other factors also are studied.

Furthermore, there is a "chicken-and-egg" question. Even if antibiotic use is causally linked to future allergic disease, it is not clear which is the cause and which is the effect. It is conceivable that children who are destined to develop allergies in the second and subsequent years of life already have pre-clinical changes in inflammatory responses and mucosal anatomy that make them more likely to develop respiratory infections (and, thus, to receive antibiotic treatment) early in life.

So, these new data are intriguing. It is possible that the link between antibiotic use and allergies is causal; but, further studies will be needed to prove that. In the meantime, the authors of this study wisely advised that antibiotics only be used in infants when there is clear clinical benefit. Antimicrobial stewardship is important, whether antibiotics cause future allergies or not. ■

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ABSTRACT & COMMENTARY

Rotavirus Vaccine and Intussusception

By Dean L. Winslow, MD, FACP, FIDSA

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: Using active surveillance, researchers enrolled 717 infants with intussusception from sub-Saharan Africa. The risk of intussusception was no higher in those who received the monovalent rotavirus vaccine than in non-immunized infants.

SOURCE: Tate JE, Mwenda JM, Armah G, et al. Evaluation of intussusception after monovalent rotavirus vaccination in Africa. *N Engl J Med* 2018;378:1521-1528.

Monitoring of intussusception rates was instituted at 29 sentinel hospitals in seven sub-Saharan African countries (Ethiopia, Ghana, Kenya, Malawi, Tanzania, Zambia, and Zimbabwe) to assess the safety of a newly introduced monovalent rotavirus vaccine (RV1). Patients were enrolled from 2012-2016. Researchers employed standardized criteria for the diagnosis of intussusception and standardized case reporting. The incidence of intussusception was analyzed at days 1-7 (corresponding to peak viral replication), days 8-21, and days 1-21 following RV1 vaccination.

Researchers identified 717 patients with confirmed intussusception following vaccination in children 28-245 days of age. One case occurred in the one- to seven-day time period after dose 1, and six cases occurred in the eight to 21 days after dose 1. Five cases occurred in the one to seven days after dose 2, and 16 cases occurred in the eight to 21 days after dose 2. The relative risk of intussusception was 0.25 following dose 1 and 0.76 following dose 2. The rate was far below the background rate of intussusception.

■ COMMENTARY

The initial rotavirus vaccine (RotaShield) was associated with one excess case of intussusception per 10,000 children when first introduced into high- and middle-income countries and was withdrawn from the market.[1] Newer monovalent (Rotarix) and pentavalent (RotaTeq) vaccines subsequently were released and, although licensing studies did not show an excess incidence of intussusception associated with the administration of the newer vaccines, post-marketing surveillance suggested one to six excess cases of intussusception per 100,000 immunized children in high- and middle-income countries.[2]

Little data exist on efficacy and safety of rotavirus vaccine when used in children in the developing world. Since more than half of the childhood deaths due to rotavirus infection occur in sub-Saharan Africa, this large, well-conducted study that did not show excess rates of intussusception should be reassuring and supports the more widespread rollout of rotavirus vaccine in the developing world. ■

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ABSTRACT & COMMENTARY

VRE and MRSA: Time to Assign Contact Precautions to the Dust Heap of History

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: In the context of other horizontally implemented, effective infection prevention measures, the use of contact precautions for most patients colonized or infected with MRSA or VRE fails to provide benefit.

SOURCE: Bearman G, Abbas S, Masroor N, et al. Impact of discontinuing contact precautions for methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant Enterococcus: An interrupted time series analysis. *Infect Control Hosp Epidemiol* 2018;39:676-682.

Bearman and colleagues at the Virginia Commonwealth University evaluated the impact of seven individual horizontal infection prevention interventions implemented at various times at their 865-bed academic medical center. These were, in sequence:

- January 2011: Urinary catheter bundle implementation;
- June 2011: Chlorhexidine perineal care outside ICUs;
- March 2012: Hospital-wide chlorhexidine bathing outside ICUs (implemented in ICUs in 2007);
- April 2013: Discontinuation of contact precautions for methicillin-resistant *Staphylococcus aureus* (MRSA) or vancomycin-resistant Enterococcus (VRE) colonization or infection (absent draining wounds not contained with a bandage);
- August 2014: Monitoring of compliance with contact precautions (still existing for other pathogens) and with "bare below elbows" (initiated in 2009);
- March 2015: Use of ultraviolet-C disinfection robot;
- March 2016: Automatic urinary catheter discontinuation at 72 hours.

Changes in infection rates in association with the interventions were assessed by segmented regression modeling. Hospital-acquired infection (HAI) rates decreased throughout the period

analyzed. Following the discontinuation of contact precautions for VRE and MRSA, the rate of HAI due to MRSA decreased by 1.31 per 100,000 patients, while VRE HAI decreased by 6.25 per 100,000 patients; neither change was statistically significant. The rate of both combined fell by 7.56 per 100,000 patients (P = 0.21), while the rate of device-associated infections decreased by 2.44 per 100,000 patients (P = 0.23).

■ COMMENTARY

Based largely on observational studies involving outbreaks in which contact precautions were generally a part of a multifaceted bundle of interventions, since 2007 the CDC has recommended the use of personal protective equipment (PPE) during contact with patients either infected or colonized with multidrug-resistant organisms, including both VRE and MRSA. The recommended PPE includes gloves and isolation gowns. However, recent studies have strongly suggested that this admonition is, at best, ineffective, and, at worst, harmful.

Bearman and colleagues provided further evidence that it may be time to end the practice of contact precautions for all patients infected or colonized with VRE or MRSA. This is not a new concept and, in fact, has been addressed previously in *Infectious Disease Alert*.[1] I concluded the commentary at that time in the following way: "Overall, a reasonably firm conclusion can be reached that routine contact isolation for endemic MRSA and VRE is unnecessary (and may be harmful) when there is active maintenance of hand hygiene, environmental cleaning, and chlorhexidine bathing." The results examined here, which are consistent with those of several other recently published studies, strongly confirm this conclusion. Thus, a 2018 systematic review and meta-analysis concluded that discontinuation of contact precautions for MRSA and VRE has not been associated with increases in infection rates.[2] I believe it is time to accept the evidence and act accordingly. ■

[Bearman and colleagues provided further evidence that it may be time to end the practice of contact precautions for all patients infected or colonized with VRE or MRSA.]

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ABSTRACT & COMMENTARY

Reduced Noninfectious Adverse Events After Discontinuation of Contact Precautions in Patients Colonized or Infected With MRSA and/or VRE

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: Discontinuation of contact precautions for patients colonized or infected with either MRSA or VRE is associated with a decrease in rates of noninfectious adverse events.

SOURCE: Martin EM, Bryant B, Grogan TR, et al. Noninfectious hospital adverse events decline after elimination of contact precautions for MRSA and VRE. *Infect Control Hosp Epidemiol* 2018 May 10:1-9. doi: 10.1017/ice.2018.93. [Epub ahead of print].

In 2016, Martin and colleagues at UCLA and the Santa Monica Hospital reported that elimination of routine contact precautions for endemic methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant Enterococcus (VRE) infection or colonization was not associated with an increase

in detection of these organisms, but was associated with considerable cost savings. Others have confirmed a lack of adverse outcomes resulting from discontinuation of contact precautions in response to these organisms,[1,2] indicating that this strategy is safe. The same group now reports that this approach is not only safe, but it is associated with a reduction of noninfectious adverse events.

In a before-and-after study, the investigators compared hospital reportable adverse events for single years prior to and after discontinuation of contact precautions for VRE and MRSA. During the year before, chlorhexidine bathing for almost all inpatients was implemented. The noninfectious adverse events that were considered were postoperative respiratory failure, hemorrhage/hematoma, thrombosis, wound dehiscence, pressure ulcers, and falls or trauma. The comparison was analyzed using segmented and mixed-effects Poisson regression models.

Approximately 12% of 24,732 admissions in the pre-intervention period resulted in isolation for MRSA and/or VRE, while no patient was isolated for this reason post-intervention. Meanwhile, there was an overall 19% decrease in noninfectious adverse events from pre- to post-intervention from 12.3 per 1,000 admissions to 10.0 per 1,000 admissions ($P = 0.022$). There was no significant change in overall infectious adverse events. Limiting the analysis to MRSA/VRE admissions, the rate of noninfectious adverse events decreased from 21.4 per 1,000 to 6.08 per 1,000 admissions ($P < 0.001$) — a 72% reduction.

■ COMMENTARY

The authors of several studies have reported that patients may suffer from a wide variety of adverse events as a result of being placed in contact precautions. However, recent studies have contradicted these findings. This study has some of the usual drawbacks of most infection prevention research, including its quasi-experimental before-and-after design and other changes such as the implementation of almost universal chlorhexidine bathing during the pre-intervention period.

Several studies indicate that the elimination of routine contact precautions for patients with MRSA and/or VRE colonization or infection is safe (i.e., not associated with increased rates of detection of affected patients). Martin and colleagues have found that such discontinuation is not just safe regarding infection, but it actually appears to enhance patient safety as evidenced by a decrease in noninfectious adverse effects. ■

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ABSTRACT & COMMENTARY

Oral Antibiotics May Increase the Risk for Nephrolithiasis

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

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

SYNOPSIS: A case-control study found that receipt of an oral antibiotic in the preceding three to 12 months was associated with nephrolithiasis. The risk persisted up to five years, and younger patients were at increased risk.

SOURCE: Tasian GE, Jemielita T, Goldfarb DS, et al. Oral antibiotic exposure and kidney stone disease. *J Am Soc Nephrol* 2018;29:1731-1740.

Despite the miraculous benefits of antibiotics, they have risks and side effects, some of which can be quite detrimental. It is well established that antibiotics disrupt the human microbiome. There

also is evidence that patients with nephrolithiasis have an altered gut microbiome compared to those without nephrolithiasis. Therefore, Tasian and colleagues sought to determine whether receiving oral antibiotics increases a patient's risk for developing nephrolithiasis.

The investigators conducted a case-control study that used The Health Improvement Network (THIN), a database from more than 13 million patients who received care from general practitioners in the United Kingdom between 1994 and 2015. Individuals younger than 90 years of age with a diagnosis code for nephrolithiasis were included. Those with codes for infectious calculi, such as calculous pyelonephritis, were excluded. The primary exposure was receiving an oral antibiotic as an outpatient within three to 12 months of the index date (i.e., the date of nephrolithiasis diagnosis). Any antibiotic prescription of any dosage and duration within the exposure window was included.

The most common reasons for antibiotic use were chest infection, cough, upper respiratory infection, tonsillitis, and urinary tract infection (UTI). Prescriptions for all classes of oral antibiotics except lincosamides (e.g., clindamycin) were greater among patients with nephrolithiasis compared to controls. The oral antibiotics with the highest association for nephrolithiasis with no adjustment for other antibiotic use were sulfa drugs (odds ratio [OR], 2.37; 95% confidence interval [CI], 2.23-2.52), cephalosporins (OR, 1.93; 95% CI, 1.81-2.07), fluoroquinolones (OR, 1.84; 95% CI, 1.7-1.99), nitrofurantoin (OR, 1.84; 95% CI, 1.67-2.02), and broad-spectrum penicillins (OR, 1.37; 95% CI, 1.28-1.47). Treatment with antibiotics for *H. pylori* was not significantly associated with nephrolithiasis risk. The risk was greatest within three to six months from the index date for antibiotics in all five classes and remained significant for three to five years for all classes except broad-spectrum penicillins.

Furthermore, the odds ratios were greatest for antibiotic exposures at younger ages, which were seen with all five antibiotic classes. The sensitivity analysis found that when patients with a prior UTI were excluded, the magnitude of the association increased for sulfa and nitrofurantoin, decreased for broad-spectrum penicillins, and stayed the same for the other antibiotic classes.

■ COMMENTARY

During the past 30 years, the prevalence of nephrolithiasis in the United States has risen by 70%. The reasons for this spike are uncertain. One hypothesis is that it might be caused by antibiotic use. Because correlation does not always equal causality, the study by Tasian and colleagues is important because it elucidates the association between oral antibiotics and nephrolithiasis. Exposure to five common classes of oral antibiotics increased the risk for nephrolithiasis, even after adjustment for multiple confounding factors, the rate of healthcare encounters, and exclusion of patients with prior UTI. Moreover, the magnitude of the associations was strongest in younger patients. This is an important finding because children receive more antibiotics than any other age group and the incidence of nephrolithiasis has been rising fastest among children and young women. Thus, the results of this study are another reason to promote judicious antibiotic use in the outpatient setting.

[During the past 30 years, the prevalence of nephrolithiasis in the United States has risen by 70%.]

How could antibiotics increase the risk for developing nephrolithiasis? One proposed mechanism is that changes in the gut microbiota alter macronutrient metabolism, leading to increased calcium stone formation. Indeed, children might be more susceptible because antibiotic exposure at a younger age produces more profound effects on their microbiome than exposure later in life. Another potential mechanism is that antibiotics select for multidrug-resistant (MDR) pathogens that promote kidney stone formation. Prior studies have shown that up to 70% of bacteria cultured from calcium stones are MDR, and their role in stone formation needs further investigation.

There are a few limitations to the study that should be mentioned. First, the results could have been influenced by unmeasured confounding variables, such as unreported comorbid illnesses. Second, some patients may have had unrecognized, asymptomatic kidney stones before receiving their course of antibiotics. Third, only outpatient data on oral antibiotics were available, so no conclusions about the association of parenteral antibiotics and nephrolithiasis can be reached. Finally, it was presumed that patients prescribed antibiotics took them and no attempt was made to verify medication compliance.

The report by Tasian and colleagues suggests that oral antibiotics from five common classes

are a novel risk factor for the development of nephrolithiasis. These findings have important implications for both the pathogenesis of nephrolithiasis and for promoting better antibiotic stewardship in the outpatient setting. ■

ABSTRACT & COMMENTARY

Why IDSA Did Not Support the Surviving Sepsis Campaign

By Dean L. Winslow, MD, FACP, FIDSA

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

SYNOPSIS: The Infectious Diseases Society of America withheld its support for the Surviving Sepsis guidelines. The general concerns included vagueness and inconsistency in definition of sepsis, "one size fits all" prescription of time to administer antibiotics, lack of clarity around drawing blood cultures through IV catheters, recommendation of combination antibiotics, lack of definition around when to use procalcitonin levels, when and how to use pharmacokinetic and pharmacodynamic data effectively, prolonged antibiotic "prophylaxis," and duration of therapy.

SOURCE: IDSA Sepsis Task Force. Infectious Diseases Society of America (IDSA) POSITION STATEMENT: Why IDSA did not endorse the Surviving Sepsis Campaign Guidelines. *Clin Infect Dis* 2018;66:1631-1635.

An Infectious Diseases Society of America (IDSA) delegate (trained in both infectious disease and critical care medicine) served on the Surviving Sepsis Campaign writing team. Differences of opinion expressed by the IDSA delegate and the IDSA Standards and Practice Guideline Committee ultimately were not accepted by the writing committee and campaign leadership; therefore, the IDSA reluctantly withdrew its support of the new guidelines. Major areas of concern identified by IDSA in the 2016 Surviving Sepsis Campaign guidelines are summarized in the synopsis above.

■ COMMENTARY

It is clear that the Surviving Sepsis Campaign has done much to raise awareness and improve care and outcomes in patients with sepsis and septic shock. In general, the IDSA representatives (and indeed most of us practicing ID specialists) appreciate the overall goals of these guidelines to recognize sepsis promptly and to treat septic patients aggressively and rapidly with evidence-based interventions. The main points of contention between IDSA and Society of Critical Care Medicine centered on specific recommendations and the interpretation of the studies used to support these recommendations.

Since up to 40% of patients admitted to ICUs with a diagnosis of sepsis do not have an infection,[1] the benefits of treating infected patients need to be balanced against the harms of treating patients who are not infected. The new guidelines generally failed to define "sepsis," "septic shock," and "suspected sepsis/septic shock" with any degree of sensitivity or specificity. While "septic" patients with likely bacterial infection should receive antibiotics promptly, those patients with likely viral infections or noninfectious causes potentially could be harmed by administration of antibiotics. While the risk of giving antibiotics is worth taking in a patient in shock, patients with less severe illness probably should be evaluated more carefully before being given antibiotics. Our

group thought that a good analogy would be to consider "sepsis" like a hypertensive urgency, and "septic shock" like a medical emergency. Similarly, prescribing an exact time interval from initial contact to administration of antibiotics is not strictly evidence-based but should be individualized. It also is not clear from the guidelines at what point the clock starts (first detection of fever, time patient arrived in ED, time of documentation of organ dysfunction, time antibiotic is ordered, etc.).

The guidelines also are vague about recommendations on drawing blood cultures from IV lines — what type of line, how to do so without contamination, etc. The guidelines do not provide guidance on management of tunnel tract and exit site infections or infected ports, and do not specifically recommend removal of lines in patients with refractory shock, hard-to-treat organisms, or persistent bacteremia — which we recommended.

The big area we objected to was the guidelines' unsupported recommendation for "combination antibiotic therapy" in patients with both sepsis and septic shock. The guidelines jumble a lot of terms (empiric, targeted/definitive, multidrug, combination) and do not define them adequately. Particularly troublesome was their definition of "combination therapy" as multidrug regimens, which accelerate pathogen clearance, inhibit toxin production, or produce immunomodulatory effects. For this recommendation to administer combination therapy, the authors of the guidelines cited a largely discredited retrospective propensity-matched analysis. However, randomized controlled trials (including those conducted in patients with neutropenic sepsis) never have shown any benefit of combination therapy. Many of us from IDSA were very concerned that this poorly supported recommendation could lead to excessive use of toxic regimens such as β-lactams + aminoglycosides or regimens likely to lead to *Clostridium difficile* infection, such as β-lactams + fluoroquinolones.

The new guidelines mention that procalcitonin "could be used" to guide duration of therapy in patients who have "limited evidence of infection." In reality, there exists robust literature supporting the use of procalcitonin to guide duration of antibiotic therapy in patients both with and without documented infection.

The new guidelines mention using pharmacokinetic and pharmacodynamic data to optimize dosing of antibiotics, yet they provide no specific guidance on how to operationalize pharmacokinetic and pharmacodynamic data.

Although the Surviving Sepsis Campaign guidelines recommend against using "sustained systemic antimicrobial prophylaxis in patients with SIRS of noninfectious origin," it concerned us that they were recommending "non-sustained antimicrobial prophylaxis" in such patients. We were concerned that this vague and unsupported guidance actually would encourage doctors to use systemic antibiotics to "prevent infection" in ICU patients.

The new guidelines recommend that patients with sepsis or septic shock receive 7-10 days of antibiotics. We were concerned that this blanket recommendation would lead to overtreatment in many cases and undertreatment in others. For example, community-acquired pneumonia can be treated adequately in five days, intra-abdominal infections in four days with source control, yet *Staph. aureus* bacteremia often will require longer courses.

Finally, although we ultimately did not include this in our article, many of us in IDSA have serious concerns about the Surviving Sepsis Campaign's "one size fits all" guidance for IV fluid administration in patients with sepsis (not those with true septic shock). Many of us as clinicians have seen first hand the adverse effects of over-resuscitation of non-hypotensive elderly patients, often with impaired diastolic function or renal insufficiency, which has resulted in patients needing BiPap or even intubation because of iatrogenic pulmonary edema. ■

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Infectious Disease [ALERT]

Updates

By Carol A. Kemper, MD, FACP

Utility of GI Multiplex Assay

SOURCE: Cybulski RJ Jr, Bateman AC, Bourassa L, et al. Clinical impact of a multiplex gastrointestinal PCR panel in patients with acute gastroenteritis. *Clin Infect Dis* 2018 April 25; doi:10.1093/cid/ciy357.

A nine-month prospective study was launched in 2016-2017 to compare the results of the new BioFire Gastrointestinal FilmArray™ with conventional laboratory techniques in persons

with acute diarrhea. A total of 1,887 consecutive stool samples obtained from both the inpatient and outpatient setting were tested in parallel using the FilmArray and stool culture. Multiple media were used, including blood agar, MacConkey, MacConkey-sorbitol, *Salmonella-Shigella* selective media, and *Campylobacter* selective agars, as well as enhanced media for recovery of *Vibrio* spp. Additional conventional testing included ova and parasite, *Giardia* antigen, *Cryptosporidium/ Cyclospora* modified acid-fast smear, and a viral gastroenteritis PCR panel. Patients with *Clostridium difficile* detected by either FilmArray or conventional methods were excluded from the final analysis.

The FilmArray successfully identified one or more pathogens in 669 specimens (35.3%) compared with 113 specimens (6%) using conventional culture techniques. Of these 669 specimens, 155 (8.2%) were bacterial pathogens, generally isolated in culture — resulting in a 37% greater recovery of conventional bacterial pathogens by FilmArray compared with conventional methods. Of these, significantly more STEC, *Plesiomonas shigelloides*, and *Yersinia enterocolitica* were identified by PCR.

Organisms not readily captured in culture also more frequently identified by PCR included *Campylobacter* spp. and *Shigella*/Enteroinvasive *Escherichia coli* (which are indistinguishable by this array). Interestingly, the most common pathogen identified by FilmArray was *C. difficile* (25.5%). FilmArray also provided improved identification of non-bacterial pathogens, including *E. histolytica* and *Giardia lamblia*, when compared with standard ova and parasite examination (1.4% vs. 0.3%).

Co-infections also were much more readily identified using FilmArray, with multiple positive targets identified in 184 specimens (27.5% of all positive specimens). Remarkably, 38 of these involved organisms that might be isolated in culture, but only four of them were detected by culture. The remaining 115 co-infections were due to pathogens not generally isolated in culture.

Fourteen specimens were positive by culture but negative by FilmArray; 12 of these were organisms not included in the current FilmArray. These included *Aeromonas* (eight cases), *Campylobacter hyointestinalis* (three cases), and one case each of *Helicobacter pullorum*, *Salmonella enterica* (a non-typhoid species), and *Campylobacter jejuni*.

Although all specimens received between 11 p.m. and 7 a.m. were set up the following morning, the median turn-around time for FilmArray results still was only 18 hours compared with 47 hours using conventional culture techniques ($P < 0.0001$). The median time to initiation of appropriate therapy for organisms detected by FilmArray was 22 hours vs. 72 hours for conventional methods ($P < 0.0001$). Sixty percent of patients with positive stool specimens were treated with targeted therapy, indicating that physicians generally found the results clinically significant. Once results were available, treatment was discontinued in eight of nine cases identified as STEC.

[The use of gastrointestinal multiplex assays for patients with acute diarrhea provides much higher yield and more quickly than conventional techniques — at least when it's performed in-house.]

The use of gastrointestinal multiplex assays for patients with acute diarrhea provides much higher yield and more quickly than conventional techniques — at least when it's performed in-house. Thus, the FilmAssay required less labor and improved laboratory flow, but also importantly it allowed for directed rather than empiric therapy much more quickly — an important stewardship goal. However, the clinical applicability of this newer technology is still in the learning phase, as a recent case so sharply illustrated. An American returning from India was hospitalized recently at our facility with severe watery diarrhea and profound hypotension and dehydration (he had been working in the slums). He had been hospitalized in India and treated with multiple different antibiotics, including parenteral therapy, before returning to the United States. His diarrhea continued, unabated, and a GI multiplex assay obtained in the outpatient setting was positive for *Shigella*, *Giardia*, and cholera. He received ciprofloxacin and tinidazole for five days, with some improvement, and then relapsed, with 15-20 watery stools a day.

Clinically, it certainly seemed like it could be relapsed cholera, but despite repeated courses of treatment? He required admission over the Memorial Day weekend, and all cultures and conventional assays were negative, including cultures for *Vibrio*, *Shigella*, *Shigella* toxin, and *C. difficile*. A repeat multiplex assay was still positive for cholera, *Shigella*, and *Giardia*. We were left with the perplexing task of sorting out whether

this was drug-resistant cholera with relapse (and negative cultures), *Shigella* (with negative cultures and a negative toxin test), or possible *Giardia* (of course, complicated by the fact that stool O&P are now in the age of PCR, perversely, send-outs and the results delayed by five days or longer over the Memorial Day weekend), or was this something else? I don't know who was more frustrated — the patient or us — although, granted, he was the one with unrestrained diarrhea. In the end, the stool was positive for *Giardia* trophozoites — and he improved with nitazoxanide.

And as one of our internists explained to a very frustrated patient, the rest of the PCR results were just "footprints in the sand."

'The World Is Covered by a Thin Layer of Feces'

SOURCE: Janezic S, Mlakar S, Rupnik M. Dissemination of *Clostridium difficile* spores between environment and households: Dog paws and shoes. *Zoonoses Public Health* 2018, April 23: doi:10.1111/zph.12475. [Epub ahead of print].

This quote is the best line I've ever heard — by Lucy Tompkins, MD, Stanford (my infectious disease attending many years ago).

This smart little study examines the risk of acquiring *Clostridium difficile* when walking the dog (literally). The researchers examined 20 households in Eastern Slovenia with a pet dog. Five were urban households and 15 were rural. Samples from the shoes, household slippers, and dog paws were collected within 30 minutes of walking the dog or the owner returning from a walk. Duplicate samples were permitted in households with two dogs. All samples were submitted for PCR ribotyping and toxinotyping, as well as culture.

Ninety samples were collected from 20 households, including 25 from dog paws, 44 from shoes (both the right and the left), and 21 from household slippers. Of these, remarkably, *C. difficile* was detected on 31 of 90 specimens (34%) from 14 of the households (70%). *C. difficile* was isolated from 43% of shoes, 28% of slippers, and 24% of dog paws. Altogether, 465 *C. difficile* isolates were obtained and sequenced, revealing 13 different ribotypes. Half were PCR ribotype 014/020, which was found in 18 different samples collected in eight different homes. Five of these 13 different ribotypes were toxigenic.

This study fits nicely with earlier work in New York City, which found that sand boxes and dog play areas often are contaminated with *C. difficile*. Basically, *C. difficile* is all around us. But it does make me wonder about the risk of spreading *C. difficile* in the hospital on my shoes. We don't allow dogs in isolation rooms for this reason, but could my feet be a vector while I perform my daily rounds? ■

ABIM CME MOC ACCREDITED

CME INSTRUCTIONS

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CME QUESTIONS

1. Which of the following statements is true regarding antimicrobial therapy during the first six months of life?

a. It is prescribed consistently following clear, accepted indications.

b. It is linked to the development of later poor growth.

c. It is linked to the development of later allergic disease.

d. It is ineffective for otitis media.

2. Which of the following is correct regarding exposure to orally administered antibiotics and the development of nephrolithiasis?

a. The association is greatest when antibiotics are given to the elderly.

b. The association is present for only four weeks after antibiotic administration.

c. The highest association risk is with the use of antibiotics to treat *Helicobacter pylori* infection.

d. The antibiotics associated with the highest risk were sulfas, cephalosporins, fluoroquinolones, and broad-spectrum penicillins.

3. Discontinuation of routine use of isolation with contact precautions for inpatients colonized or infected with VRE and/or MRSA is associated in recent studies with which of the following?

a. An increased incidence of infection with MRSA and VRE.

b. An increased incidence of infection with MRSA but not VRE.

c. A decreased incidence of noninfectious adverse events.

d. An increased incidence of VRE but not MRSA.

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.