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Infectious Disease [ALERT]

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ABSTRACT & COMMENTARY

Probiotics Do Not Prevent *C. difficile* Infection in Hospitalized Patients

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

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

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

SYNOPSIS: A retrospective cohort study from a single California hospital found the administration of probiotics to patients receiving antibiotics did not reduce the incidence of healthcare facility-onset *Clostridioides difficile* infection.

SOURCE: Box MJ, Ortwine KN, Goicoechea M, Scripps Antimicrobial Stewardship Program (SASP). No impact of probiotics to reduce *Clostridium difficile* infection in hospitalized patients: A real-world experience. *Open Forum Infect Dis* 2018;5:ofy192.

Healthcare facility-onset *Clostridioides difficile* infection (HO-CDI), formerly known as *Clostridium difficile*, is detrimental to patients and healthcare institutions alike. Some data suggest the co-administration of probiotics with antibiotics may reduce the risk for HO-CDI, at least in institutions where the rates are high (i.e., > 20%). As part of a care bundle to reduce HO-CDI, a specific probiotic formulation was recommended for administration to patients receiving antibiotics and judged to be at high risk for HO-CDI at the authors' institution. Thereafter, the researchers sought to determine whether probiotics are beneficial in a hospital with a lower rate of HO-CDI, what they describe as a "real-world" environment.

The investigators conducted a retrospective cohort study at a 400-bed community hospital in La Jolla, CA. Patients were included if they were 18 years of age or older and had received at least one dose of antibiotics and had a length of stay longer than three days. The authors of the study excluded patients whose CDI was community-

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Infectious Disease [ALERT]

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acquired or who had received cefazolin or cefoxitin for surgical prophylaxis. The primary outcome was the incidence of HO-CDI in patients who received IV antibiotics plus probiotics compared to those who received IV antibiotics alone.

During the study period of March 29, 2016, to Sept. 30, 2016, investigators evaluated 1,576 patients treated with IV antibiotics. Of those patients, 649 received antibiotics plus probiotics and 927 received antibiotics alone. The two groups were well matched in terms of age and intensive care unit (ICU) stay. However, patients who received probiotics had significantly longer length of stay (LOS), a higher Charleston Comorbidity Index (CCI), and a higher amount of antibiotics billed. The use of acid-suppressing agents was not significantly different between the two groups.

HO-CDI occurred in 11 of 649 patients who received antibiotics plus probiotics and in eight of 927 patients who received antibiotics alone (1.8% vs. 0.9%, respectively; $P = 0.16$). The median duration of probiotic use was 8.1 days. Furthermore, in-house mortality was higher in the antibiotics plus probiotics group (53/649; 8.2%) compared to the antibiotics alone group (63/927; 6.8%), although this difference was not significant ($P = 0.32$).

The authors conducted a subgroup analysis to determine if greater exposure to antibiotics in the probiotic group offset a potential benefit. They compared HO-CDI rates in the probiotic group with rates in the top 30% of patients by antibiotic exposure (billed grams of antibiotics) in the group that received antibiotics alone. There was no observed difference in HO-CDI rates between the two groups (five of 284 patients, 1.8%; P = no significance).

■ COMMENTARY

This large, retrospective cohort study revealed no benefit for probiotics in preventing HO-CDI. The use of probiotics for CDI prevention has been controversial. The most recent Infectious Diseases Society of America guidelines decline to endorse probiotics as a CDI prevention strategy outside of clinical trials, citing insufficient data at the time of publication.[1] Based on the results of the study by Box and colleagues, their institution removed all probiotics from the formulary. This decision seems rational from a quality standpoint, since probiotics did not demonstrate any benefit and have associated costs.

[The best way forward to reduce the risk for *C. difficile* infection is through prudent and aggressive antibiotic stewardship efforts.]

There were a few limitations to the study. First, it was conducted at a single community hospital, which may limit its generalizability to other healthcare settings, such as nursing homes, or for outpatients. Second, the authors did not explore the association and outcomes between probiotics and specific antibiotics, including those that are more prone to cause CDI. Third, the retrospective design may have led to bias from unmeasured confounding factors, such as differences in probiotic prescribing by physicians. Fourth, the finding that the probiotic recipients had higher CCIs and longer LOS and received more antibiotics likely indicates they were more ill and at higher risk for CDI. This

could have skewed the results and led to a type II error. Finally, there was no attempt made to discern initial CDI from recurrent CDI. Whether probiotics had any benefit in cases of recurrence is unclear from the study data.

Antibiotic use is the most important modifiable risk factor for CDI. The CDC estimates that 30% of antibiotics are prescribed unnecessarily.[2] Thus, the study by Box and colleagues is another nail in the coffin for the idea that probiotics prevent CDI. Instead, it reaffirms that the best way forward to reduce the risk for CDI is through prudent and aggressive antibiotic stewardship efforts.

Rather than further studies on probiotics, it would be more pragmatic if investigators focused on ways to reduce antibiotic use that still leads to successful eradication of infections and positive outcomes. For example, studies that elucidate the least amount of time that antibiotics can be given for a particular infection to result in a cure would be valuable from clinical, quality, safety, and resource utilization perspectives. ■

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ABSTRACT & COMMENTARY

The Slippery Slope of Inappropriate Antibiotic Use in Children

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: Inappropriate antibiotic use for a child with a viral respiratory infection is not a "one and done" error. Children who receive antibiotics when diagnosed with a viral respiratory infection are more likely to seek care for viral infections subsequently and to receive inappropriate antibiotics again.

SOURCE: Morgan JR, Carey KM, Barlam TF, et al. Inappropriate antibiotic prescribing for acute bronchitis in children and impact on subsequent episodes of care and treatment. *Pediatr Infect Dis J* 2019;38:271-274.

Each year, children in the United States receive approximately 10 million antibiotic prescriptions for the treatment of viral respiratory infections. While this practice is ineffective against viruses, this unnecessary antibiotic use contributes to antibiotic resistance, illness due to *Clostridium difficile* infection, the development of asthma, and increased risks of obesity. Provider characteristics and parental expectations can contribute to the inappropriate prescription of antibiotics. However, the effect of one inappropriate antibiotic prescription on future prescriptions for the same child had not been studied. Morgan and colleagues evaluated the likelihood that using antibiotics for one viral infection would alter prescribing habits during subsequent viral illnesses.

Morgan and his collaborators in Boston analyzed data from the Truven Health Analytics MarketScan Commercial Claims and Encounters database from 2008 through 2015. This database includes medical claims from 350 payers for employed individuals and their dependents across the United States. From this database, researchers assembled a cohort of 14,683 children born in 2008. Each included child had at least one medical encounter with a primary diagnosis of "acute bronchitis" (ICD-9 codes 466.xx and 490) and continued to be followed through 2015. Children with complex chronic conditions and children who had secondary diagnoses that would warrant antibiotic treatment were excluded from the cohort. Investigators evaluated the data to determine if prescribing behavior during the initial viral respiratory infection was associated with subsequent medical visits for similar infections and whether antibiotics were used during those subsequent visits. Provider characteristics (geographical region, specialty, practice setting) and patient characteristics (age, gender, previous diagnosis of asthma) were noted.

Overall, 49.8% of children initially seen for a viral respiratory infection were treated with an antibiotic. Subsequently, 45% of children seen for an initial episode of bronchitis were seen later for another similar episode. Seventy-one percent of those who received an antibiotic with the first episode received an antibiotic again with the subsequent episode of a viral respiratory illness, compared with 43% of those who did not receive an antibiotic with the first viral infection. Antibiotic use during the first visit was more common among girls (48% vs. 44% in boys), in the Midwest, and in older children. Those with asthma and those treated by pediatricians were less likely to receive antibiotics.

If an antibiotic was given during the first episode of care for bronchitis, subsequent care for a similar visit was more likely (hazard ratio, 1.24), and repeat antibiotic use was more likely (hazard ratio, 2.13). Children with asthma were less likely to receive an antibiotic at the next visit for a viral respiratory infection.

Thus, the initial healthcare interaction for a viral respiratory infection was predictive of the risk for future visits and for subsequent antibiotic use. Specifically, those who inappropriately received an antibiotic at the first visit were more likely to return with a subsequent similar illness and were more likely to receive an inappropriate antibiotic prescription again.

■ COMMENTARY

During the past century, antibiotic use has reduced the morbidity and mortality of infections in children dramatically. Now, however, we are seeing problems from inappropriate overuse of antibiotics.

In discussing the limitations of their study, Morgan and colleagues acknowledged that they could not evaluate the accuracy of the diagnoses recorded in the claims database. However, they were careful to include only codes that are typical for viral infections (bronchitis, bronchiolitis, chest cold, laryngotracheobronchitis), and they were careful to exclude children with concurrent secondary diagnoses of bacterial infections (otitis media, pneumonia). Their database only included insured children of employed parents, so it might not yield results that are representative of all American children. Nonetheless, these limitations do not diminish the importance of a major finding in this study: Approximately half of children seen by a physician for a viral respiratory infection and no documented evidence of bacterial disease were treated with an antibiotic.

[Misuse of antibiotics carries consequences for individual patients and for populations, and inappropriate care risks replication.]

Whatever the (inappropriate) reason for giving an antibiotic with the initial episode of a viral respiratory infection, that initial decision to use an antibiotic seems to have been a step down a slippery slope that led to an increased risk of using medical resources (visits, antibiotics) during subsequent episodes of viral respiratory infection. Misuse of antibiotics carries consequences for individual patients and for populations, and inappropriate care risks replication. The challenge before physicians caring for children with viral respiratory infections was well summarized more than a decade ago in the *New England Journal of Medicine*: "Withholding therapy is much more difficult than giving it."[1] It still is better to do what is right for the child, even if that means not writing an antibiotic prescription.

Overuse of antibiotics is not just a local problem for someone else. Although there were geographic variations noted by Morgan et al, antibiotic over-prescription is common throughout the United States. Recent data also show that antibiotic use is a global problem. In Papua New Guinea, 82% of children treated for a "common cold" received antibiotics, even though healthcare providers acknowledged the viral etiology of the illness.[2] Whether in the United States or New Guinea, antibiotic overuse is common.

Morgan noted that pediatricians were slightly less likely to give antibiotics for viral respiratory infections than were other physicians. Earlier this year, Poole and colleagues reported a comparison of antibiotic prescribing habits in U.S. emergency departments.[3] They noted that emergency departments staffed by non-pediatric providers were more likely to prescribe antibiotics than were pediatric emergency departments. Also, non-pediatric emergency departments were twice as likely to use macrolides rather than more specific, targeted antibiotics. Poole encouraged a wider spread of pediatric antibiotic stewardship efforts.[3]

Similarly, this year Papenburg and colleagues reported about bronchiolitis management in emergency departments.[4] They sampled 612 children younger than 2 years of age who were treated for bronchiolitis in an emergency department. Of those children, 12% had an identified bacterial co-infection, but 26% of the children were treated with antibiotics. The rate of overuse of antibiotics did not decline during the nine years of that study. The authors astutely noted that, "Antibiotic use did not decrease after national recommendations against routine prescribing." They suggested that "efforts are needed to reduce unnecessary and inappropriate antibiotic use for bronchiolitis."[4]

The data are clear — antibiotics are prescribed inappropriately for viral respiratory tract infections in children in the United States and around the world. The recommendations are also clear — antibiotics should not be used for viral infections. Our efforts toward judicious antibiotic use and wise antibiotic stewardship should continue. ■

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ABSTRACT & COMMENTARY

Sleep Tight, Don't Let the *Mucorales* Bite

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: *Mucorales* were found to commonly contaminate linen delivered to 15 transplant and cancer centers in the United States.

SOURCE: Sundermann AJ, Clancy CJ, Pasculle AW, et al. How clean is the linen at my hospital? The *Mucorales* on unclean linen discovery study of large United States transplant and cancer centers. *Clin Infect Dis* 2019;68:850-853.

In response to prior reports of hospital outbreaks of *Mucorales* infection associated with contaminated linen, Sundermann and colleagues set out to examine the frequency of such contamination at 15 U.S. transplant and cancer centers. Members of their group met linen delivery trucks at each hospital and immediately performed contact cultures. Healthcare linens (HCL) from a laundry were considered "hygienically clean" if *Mucorales* were not recovered from > 90% of items tested.

Visual contamination with lint, hair, insects, or other material was detected on five (33%) HCL on their arrival at the hospital, while this was true of three (20%) laundry carts. *Mucorales* was detected by culture of newly delivered HCL at seven (47%) hospitals. HCL were deemed not to be hygienically clean for these organisms based on the 90% rule at three (20%) hospitals. The proportion of contaminated HCL at individual hospitals ranged from none to 12/49 (24%). Culture positivity was associated with visually evident contamination and with high ambient relative humidities.

Repeat cultures over a seven-month period at a single hospital found that a median of 14% (range: 3-27%) of HCLs tested were positive. Other fungi recovered included, in decreasing order of frequency, *Aspergillus*, dematiaceous molds, and *Fusarium*. A marked decrease in frequency of *Mucorales* recovery

was observed after routine cleaning of HCL carts and lint control measures were introduced.

■ COMMENTARY

At least three hospital outbreaks of *Mucorales* infections traced to contaminated HCL and/or carts have been reported, with infections involving the respiratory tract and skin. Nonetheless, as Sundermann and colleagues indicated in their discussion, the CDC has concluded that, while contaminated fabrics and textiles can be a source of infection, "the overall risk of disease transmission during the laundry process likely is negligible" and they do not recommend routine microbiological testing of HCL.

However, some third-party certification programs currently require performance of microbiological testing by hospital laundries. Whether the decrease in contamination was causally related to implementation of the measures described by Sundermann et al is uncertain, given the known variability of prevalence of *Mucorales* and other filamentous fungi.

California has taken a different approach, recently encoding in law (Title 22, Subsection 70825) a requirement that hospital linens be washed with an effective soap or detergent and rinsed thoroughly to remove soap or detergent and soil. Linens shall be exposed to water at a minimum temperature of 71 degrees C (160 degrees F) for at least 24 minutes during the washing process. Whether this would be effective in preventing outbreaks of fungal infections is uncertain. ■

ABSTRACT & COMMENTARY

Adenovirus and CNS Disease in Children

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: Forty-eight immunocompetent children with adenovirus-associated central nervous system disease were described. Thirty-eight percent of patients died or experienced permanent neurologic sequelae.

SOURCE: Schwartz KL, Richardson SE, MacGregor D, et al. Adenovirus-associated central nervous system disease in children. *J Pediatr* 2019;205:130-137.

Forty-eight immunocompetent children (10 from Toronto's Hospital for Sick Children [SickKids] and 38 from the literature) with adenovirus-associated central nervous system (CNS) disease were reviewed. Twenty-six children with adenovirus-associated uncomplicated febrile seizures identified from the SickKids database were not included in the final analysis. Cases were identified by culture, PCR, or electron microscopy in blood, cerebrospinal fluid (CSF), or respiratory or gastrointestinal samples; other cases were identified by serologic testing. In 15% of cases, adenovirus was detected in the CSF or brain tissue, but CSF or brain tissue was not tested in all cases. The median age of the 48 children included in the analysis was 2 years, and 19 (40%) of them were female. Fever was documented in 45 (94%) children.

The most common prodromal symptoms were upper respiratory illness (23; 48%), followed by vomiting (11; 22%) and diarrhea (9; 19%). Pneumonia was diagnosed in 24 (50%). During hospitalization, hepatitis developed in 19 (40%) children and coagulopathy developed in seven (15%) children. Ten of the 48 (21%) children died and eight (17%) experienced permanent neurologic impairment, including five of the eight cases of encephalitis treated at SickKids.

By univariate analysis, factors identified by researchers that were associated with death or neurologic sequelae included younger age (1.5 vs. 2.7 years), coagulopathy, and seizures. Meningismus (presumably associated with the aseptic meningitis cases) was associated with full recovery. After adjusting for multiple variables, the only variable associated with poor outcome that retained statistical significance was the presence of seizures.

A closer look at the eight children from SickKids with adenovirus encephalitis revealed that four of eight had normal CT scans, but all had abnormal MRIs. Three of the four children with normal CT scans experienced full recovery. Neurologic sequelae seen

in the other patients included profound impairment, global developmental delay, mild cognitive impairment, dystonia, and seizures.

■ COMMENTARY

The small number of patients presented in this case series suggests that adenovirus is a relatively rare cause of CNS disease in immunocompetent children. The absolute incidence of serious neurologic disease in children with adenovirus infection is unclear because most children with adenovirus infection are not hospitalized and they seldom are tested for specific viral pathogens.

The SickKids experience and literature review show that adenovirus-associated CNS disease displays a spectrum from transient complex partial seizures or transient infection-associated encephalopathy to severe encephalitis including necrotizing encephalopathy. It is likely that direct cytopathic effect of virus occurs in many cases. However, the 15% success in detecting adenovirus in CSF or brain tissue suggests strongly that it is likely that T-lymphocyte-mediated inflammation (as demonstrated in murine models) may be important.[1] ■

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ABSTRACT & COMMENTARY

Staphylococcus aureus on the Playground and in the Gym — Is It Inescapable?

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: *Staphylococcus aureus*, including methicillin-resistant *S. aureus*, is a frequent surface environmental contaminant on both children's playgrounds and in adult fitness centers.

SOURCES: Thapaliya D, Kadariya J, Capuano M, et al. Prevalence and molecular characterization of *Staphylococcus aureus* and methicillin-resistant *S. aureus* on children's playgrounds. *Pediatr Infect Dis J* 2019;38:e43-e47.

Dalman M, Bhatta S, Nagajothi N, et al. Characterizing the molecular epidemiology of *Staphylococcus aureus* across and within fitness facility types. *BMC Infect Dis* 2019;19:69.

A group of investigators examined environmental contamination by *Staphylococcus aureus* in two distinct settings in Ohio, one potentially affecting children and the other affecting adults. They collected 280 environmental samples from 10 playgrounds in northeast Ohio over three days in July 2016. Researchers recovered *S. aureus* in culture from 89/280 (31.8%) samples, including 78/280 (27.8%) with methicillin-susceptible *S. aureus* (MSSA) and 11/280 (3.9%) with methicillin-resistant *S. aureus* (MRSA). The highest proportion of *S. aureus*-positive samples within a site was 70.4%, while that of MRSA was 11.1%; MRSA was not detected at 3/10 sites. The equipment most frequently colonized with MRSA were crawl tubes (15.0%), followed by spring riders (11.1%) and slide edges (10.5%).

The investigators also obtained 18 environmental samples from each of 16 fitness facilities in northeastern Ohio and found an overall *S. aureus* prevalence of 38.2% (110/288). MSSA was detected in 77/288 (26.7%) cultures, while 33/288 (11.5%) cultures yielded MRSA. All types of fitness facilities, including hospital gyms, had a similar prevalence of contamination with *S. aureus*, but community gyms had the highest prevalence of MRSA detection.

■ COMMENTARY

While much of the community acquisition of these organisms is believed to occur as the result of direct human-to-human contact, these results illustrate environmental sources for potential acquisition of both MSSA and MRSA in the community. If, indeed, environmental contamination leads to transmission to humans, the results demonstrate the need for improved environmental microbial control — something perhaps more easily accomplished in

fitness centers than at playgrounds. How do you routinely decontaminate a child's crawl tube? The fitness centers also present problems; all equipment types tested were implicated, including, e.g., 10/16 (62.5%) weight balls and 9/16 (56.3%) weight plates.

[All types of fitness facilities, including hospital gyms, had similar prevalence of contamination with *S. aureus*.]

The Centers for Disease Control and Prevention recommends the following for preventing transmission of *S. aureus* from the environment:[1]

- Use barriers, like a towel or clothing, between your skin and the surface.
- Shower immediately after activities in which you have direct skin contact with people or shared surfaces or equipment, such as after exercising at a health club.
- Clean your hands regularly with soap and water or an alcohol-based sanitizer.
- Keep cuts and scrapes clean and covered with bandages or dressings until healed. ■

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Baloxavir Marboxil (Xofluza)

By Abraham Chang, PharmD

Clinical Pharmacist, Stanford Health Care, Pharmacy Department

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

Baloxavir marboxil is a novel, oral, antiviral agent approved by the Food and Drug Administration (FDA) on Oct. 24, 2018, for the treatment of acute uncomplicated influenza in patients 12 years of age and older who have been symptomatic for no more than 48 hours. Baloxavir marboxil is converted by hydrolysis to baloxavir, which is a cap-dependent endonuclease inhibitor that results in inhibition of influenza virus replication. Because of the novel mechanism of action, the drug is effective against influenza strains with neuraminidase resistance.[1,2,3]

In the randomized, double-blind, placebo- and active-controlled, Phase III CAPSTONE-1 trial, investigators compared baloxavir to placebo and oseltamivir in patients 12 years of age and older with influenza A or B. The primary endpoint was time to alleviation of symptoms, which was similar to that of oseltamivir (53.5 hours vs. 53.8 hours) and significantly shorter than placebo (53.7 hours vs. 80.2 hours; $P < 0.0001$). The median time to cessation of viral shedding was significantly shorter with baloxavir compared to placebo (24 hours vs. 96 hours; $P < 0.0001$) or oseltamivir (24 hours vs. 72 hours; $P < 0.0001$).[4]

In the CAPSTONE-2 study, researchers compared baloxavir to placebo and oseltamivir in influenza patients with at least one higher risk factor defined by the Centers for Disease Control and Prevention (CDC). The primary endpoint was time to improvement of influenza symptoms, which was significantly shorter with baloxavir compared to placebo (73.2 hours vs. 102.3 hours; $P < 0.0001$), and similar to oseltamivir (81.0 hours; $P = 0.8347$). In influenza B, the time to improvement of influenza symptoms was significantly shorter with baloxavir compared to oseltamivir (74.6 hours vs. 101.6 hours; $P = 0.0251$). The median time to cessation of

viral shedding was 48 hours, which was significantly shorter than 96 hours for both placebo and oseltamivir patients.[5]

RESISTANCE

Baloxavir resistance has been observed in the clinical trials. In patients with paired sequenced samples, PA I38T/M amino acid substitutions were found in 9.7% of 370 patients who received baloxavir. No amino acid substitutions were detected in the 95 randomly selected patients who received placebo. Other mutations in PA were detected in approximately 8% of baloxavir and placebo recipients, but their effect has not been assessed. Viral shedding was detected on day 5 in 91% of patients with PA I38T/M virus compared to just 7% in patients without PA substitution.[1,2,3]

PHARMACOKINETICS

Baloxavir marboxil is a prodrug that is converted almost completely to its active metabolite, baloxavir, after oral administration. Food decreases the absorption of baloxavir, but there is no specific recommendation from the manufacturer about administration with or without food. Polyvalent cations (calcium, aluminum, magnesium) may form a chelate with baloxavir, so avoiding co-administration with dairy products, antacids, and oral supplements is recommended.[1,2] (*See Table 1.*)

No clinically significant changes in the pharmacokinetics of baloxavir and metabolites were observed with CYP3A4 inhibitors, P-gp inhibitors, or UGT inhibitors.[1]

DOSAGE AND ADMINISTRATION

Baloxavir marboxil is given in a single oral dose based on patient weight as noted in Table 2.

The medication should be administered within 48 hours of the start of influenza symptoms and can be administered with or without food. Co-administration with dairy products, antacids, and oral supplements should be avoided because of possible chelate formation.

No dose adjustments are required in the presence of a creatinine clearance (CrCl) as low as 50 mL/min or in the presence of mild hepatic impairment (Child-Pugh Class B), but the effects of more severe renal or hepatic impairment have not been evaluated.[1]

Table 1. Baloxavir Pharmacokinetics

Absorption	Tmax = 4 hours Food decreases Cmax 48%, decreases AUC 36%
Distribution	Protein binding 92.9-93.9% Volume of distribution ~1,180 L
Elimination	Half-life 79.1 hours Major route of elimination = metabolism
Metabolism	UGT1A3, CYP3A4
Excretion	Excreted in urine 14.7% Excreted in feces 80.1%

Table 2. Baloxavir Dosage

Patient body weight (kg)	Recommended oral dose
40 to 80 kg	40 mg
≥ 80 kg	80 mg

ADVERSE EFFECTS

Baloxavir is well-tolerated in clinical trials. In the Phase III study, adverse events were reported in 20.7% of baloxavir, 24.6% of placebo, and 24.8% of oseltamivir recipients. The most common adverse event was diarrhea (3.0%).

PREGNANCY AND LACTATION

There are no data on administration of baloxavir marboxil in pregnant women. In animal studies, no adverse developmental effects were observed in rats or rabbits with oral administration of baloxavir marboxil at exposure levels approximately five (rats) and seven (rabbits) times the systemic baloxavir exposure at the maximum recommended human dose.[1]

There are no data on the presence of baloxavir marboxil in lactating females. Baloxavir and its related metabolites were present in the milk of lactating rats.[1]

Table 3. Average Wholesale Price of Baloxavir and Neuraminidase Inhibitors

Agent	Unit	Average Wholesale Price
Baloxavir	20-mg tablet x 2 therapy pack 40-mg tablet x 2 therapy pack	$180 $180
Peramivir	200 mg vials x 3	$1,140
Zanamivir	5-mg blister powder for inhalation x 20 + Diskhaler inhalation device	$70.80
Oseltamivir	75 mg capsules x 10 30 mg capsules x 10	$154.57 $123.86

CONCLUSIONS

Baloxavir has similar efficacy to oseltamivir for time to alleviation of symptoms and superior efficacy to placebo in uncomplicated influenza patients. In high-risk patient populations, baloxavir was found to have a faster time to alleviation of symptoms compared to oseltamivir in influenza B patients. It is well-tolerated, oral, and administered as a one-time dose. Because of its novel mechanism of action, it has activity in influenza strains with neuraminidase resistance. Further studies are ongoing to characterize baloxavir's efficacy in hospitalized and other high-risk patient populations and as a combination with a neuraminidase inhibitor. Treatment-emergent resistance has been reported and should be considered when using this agent.

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Infectious Disease [ALERT]

Updates

By Carol A. Kemper, MD, FACP

Imagine: Multidrug-Resistant GC

SOURCE: Blank S, Daskalakis DC. *Neisseria gonorrhoeae* – Rising infection rates, dwindling treatment options. *N Engl J Med* 2018;379:1795-1797.

The United States spends an estimated $182 million annually on the treatment of acute gonococcal infection (GC) (in 2017 dollars). Imagine what would happen to that dollar figure if we lost ceftriaxone as effective therapy for GC.

The Gonococcal Isolate Surveillance Program (GISP) was begun in 1986 to monitor antibiotic resistance in *Neisseria gonorrhoeae* isolates at selected sites throughout the United States. The first evidence of a serious shift in susceptibility patterns occurred in 2007, with evidence of increasing resistance to fluoroquinolones, along with reports of clinical treatment failure. As a result, fluoroquinolones were removed from recommended treatment guidelines for GC. Subsequently, increasing MICs to cefixime and other oral cephalosporins were observed, and clinical failures to these agents began to appear. Over the past few years, increasing MICs to azithromycin have been observed.

Presently, resistance to ceftriaxone in the United States remains limited to a handful of cases. Fortunately, all isolates with reduced susceptibility to azithromycin have retained sensitivity to ceftriaxone. Although ceftriaxone retains its efficacy for now, the threat of evolving resistance to what is virtually the only remaining reliable therapy looms on our doorstep. Should this occur, it is not at all clear what the best treatment regimen might be — and it may just require days of parenteral treatment.

This editorial underscores the threat by laying out the possible consequences of a further shift in gonorrhea susceptibility patterns: 1) younger, sexually active people will be affected disproportionately, potentially resulting in lost wages and even days of hospitalization; 2) increasing risk of refractory pelvic

inflammatory disease in young women, with resulting infertility; 3) increasing risk to pregnant women and neonates, with serious health consequences and adverse pregnancy outcomes (e.g., blindness in neonates); 4) the use of potentially more toxic agents; 5) an increase in HIV infection; and 6) a stunning increase in the annual cost of STD treatment. Safe and reliable agents are needed urgently for the treatment of GC.

A New *Borrelia* Species in the 'Old World'

SOURCE: Qiu Y, Nakao R, Hang'ombe BM, et al. Human Borreliosis caused by a New World relapsing fever *Borrelia*-like organism in the Old World. *Clin Infect Dis* 2018; Nov 13. doi:10.1093/cid/ciy850. [Epub ahead of print].

While Lyme disease gets all the press, other species of *Borrelia* can cause significant and sometimes more severe disease. In Africa, relapsing fever is listed in the top 10 causes of mortality in children and is an important cause of perinatal mortality. Research into the evolutionary development of different *Borrelia* species often identifies which species are "New World" and which ones are "Old World." However, the story may be complicated by bird and bat species migration, which may play a role in the distribution of these organisms around the world.

As a brief summary, in the New World, epidemic relapsing fever is caused by the louse-borne *Borrelia recurrentis*, whereas endemic relapsing fever is caused by three different tick-borne *Borrelia* species (*B. hermsii*, *B. parkeri*, and *B. turicatae*, of which the former is the most common). In the Old World, tick-borne relapsing fever generally is caused by *B. duttonii* or *B. crocidurae*, which are recognized causes of relapsing fever, especially in West Africa. However, it has been suspected that other *Borrelia* species may play a role in relapsing fever in Africa, and other previously unrecognized species have been found in bats.

These authors reported the isolation of a novel *Borrelia*-like organism from the blood of a 35-year-old man in Zambia, the first time a *Borrelia*-like organism has been identified as a cause of "relapsing fever" in southern Africa. The young man had entered a cave in Zambia about eight days prior to developing fever, muscle aches, headache, and lassitude. One day later, he presented to the University of Zambia, where a basic workup, including a blood smear for parasites and malaria, was negative. He reported exposure to bats and a "soft tick bite."

Suspecting a possible zoonotic infection, healthcare providers took blood samples prior to initiation of antibiotics and performed cultures on specialized media (BSK). Molecular testing of blood samples also was performed. The testing isolated a spirochete, and preliminary identification by 16s rDNA and *flab* analysis suggested a *Borrelia*-like organism. The patient quickly responded to orally administered erythromycin.

The authors then turned their attention to various bat species found in the cave and their ticks. Fifty ticks were collected from the cave, all of which were identified as *Ornithodoros faini*, a soft tick. These were subjected to molecular analysis, yielding 20 ticks positive for a *Borrelia* organism. Subsequent 16S rDNA PCR and sequencing identified an organism remarkably similar to the patient's isolate (99.6-100% homology). Organ samples of bats previously collected from the cave and stored (for other purposes), as well as blood samples from 38 bats found in the cave, all were tested similarly. Twenty-seven percent yielded a similar organism. Phylogenetic analysis demonstrated the new organism, designated Candidatus *B. faini* in this study, was remarkably similar to *B. recurrentis*, despite the fact that the organism was isolated in Africa.

With the use of various molecular methods, many newer species of *Borrelia*-like organisms are being discovered throughout the world. Some reports suggest that tick ranges and distribution may be affected by climate change — and especially the prolonged droughts in Africa. But it is important to remember that tick-borne infections may occur rarely in travelers returning from Africa. ■

ABIM CME MOC ACCREDITED

CME INSTRUCTIONS

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CME QUESTIONS

1. Approximately how many children are prescribed antibiotics for the treatment of viral respiratory infections in the United States each year?

a. 100,000 to 2 million

b. 4 million to 8 million

c. 9 million to 12 million

d. 14 million to 18 million

2. Which of the following is correct regarding children with adenovirus infections of the central nervous system, based on the review by Schwartz and colleagues?

a. The frequency of prodromal upper respiratory illness was 10%.

b. The frequency of prodromal diarrhea was 80%.

c. All of the 48 patients survived.

d. One-half of the patients developed pneumonia.

3. Which of the following is correct regarding baloxavir?

a. It inhibits influenza virus neuraminidase.

b. Cross resistance with oseltamivir is frequently identified.

c. It is given twice daily for three days.

d. It has a serum elimination half-life of approximately 80 hours.

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.