formulations, making it possible to switch from an intravenous to oral route in the outpatient setting, whereas, the once-daily administration of daptomycin makes it attractive for outpatient parenteral antibiotic therapy.[5]

In conclusion, additional clinical trials are needed to evaluate the efficacy of TMP-SMZ therapy for children with acute osteomyelitis.

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REFERENCES

1. Messina AF, Namtu K, Guild M, et al. Trimethoprim-sulfamethoxazole therapy for children with acute osteomyelitis. *Pediatr Infect Dis J*. 2011;30:1019–1021.
2. Markowitz N, Quinn EL, Saravolatz LD. Trimethoprim-sulfamethoxazole compared with vancomycin for the treatment of *Staphylococcus aureus* infection. *Ann Intern Med*. 1992;117:390–398.
3. Proctor RA. Role of folate antagonists in the treatment of methicillin-resistant *Staphylococcus aureus* infection. *Clin Infect Dis*. 2008;46:584–593.
4. Esposito S, Bassetti M, Borre' S, et al.; Italian Society of Infectious Tropical Diseases; International Society of Chemotherapy. Diagnosis and management of skin and soft-tissue infections (SSTI): a literature review and consensus statement on behalf of the Italian Society of Infectious Diseases and International Society of Chemotherapy. *J Chemother*. 2011;23:251–262.
5. Leone S, Gregis G, Noviello S, et al. Comment on: outpatient parenteral antibiotic therapy (OPAT) for bone and joint infections: experience from a UK teaching hospital-based service. *J Antimicrob Chemother*. 2011;66:2682–2683.

Reply:

We thank Drs. Pezone and Leone for their letter regarding our study in which we describe our experience using trimethoprim-sulfamethoxazole (TMP-SMX) for the treatment of osteomyelitis. We share the concern that TMP-SMX has shown inferiority to vancomycin 1 when used to treat bacteremia; however, it is unclear whether the findings suggested in the study by Markowitz et al.[1] can be extrapolated to osteomyelitis in children. In addition, as noted, all of the patients in our study with methicillin-resistant *Staphylococcus aureus* (MRSA) isolated from invasive sites were first treated with vancomycin (from 1 to 26 days). Even our 1 patient who had documented MRSA bacteremia and was treated with only 1 day of vancomycin before changing to intravenous TMP-SMX recovered nicely. We also note that 1 distinct disadvantage of TMP-SMX is that is does not cover *Streptococcus pyogenes*. This does create a problem in osteomyelitis cases in which cultures from invasive sites are negative. In these cases, empiric therapy must be used and patients monitored closely for antibiotic failure. Accordingly, in any case of severe disease in which the patient is unstable, we would not recommend TMP-SMX as a first-line option. However, given a stable patient who can be closely monitored for signs and symptoms of therapeutic failure, we felt comfortable with this empiric choice given the very small number of cases of *S. pyogenes*–related osteomyelitis we see in our population.

Although first-line treatment of MRSA infections are beta-lactam antibiotics, we often discovered that there were situations in which our patients could not tolerate oral beta-lactam drugs, either due to adverse reactions or compliance issues. For example, cephalexin is sometimes a challenge for patients because it must be dosed every 6 hours. Typically, we administer TMP-SMX every 8 hours, which improves compliance. Finally, daptomycin is certainly a possible outpatient alternative. However, we strive to choose oral drugs as first-line therapy for our outpatients, thus eliminating central line–related complications.[2] Linezolid, although available in oral form, is often not approved by medical insurers and is prohibitively expensive for most of our patients to afford out-of-pocket. In addition, its long-term use is sometimes problematic due to its bone marrow suppressive side effects. Again, we thank Drs. Pezone and Leone for their comments. We also agree that additional trials are needed to evaluate the efficacy of TMP-SMZ in acute osteomyelitis.

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REFERENCES

1. Markowitz N, Quinn EL, Saravolatz LD. Trimethoprim-sulfamethozazole compared with vancomycin for the treatment of *Staphylococcus aureus* infection. *Ann Intern Med*. 1992;117:390–398.
2. Berman DM, Amin D, Namtu K, et al. Pediatric outpatient parenteral antimicrobial therapy resulting in frequent emergency center visits [presentation 1127]. In: 47th Annual Meeting of the Infectious Diseases Society of America (IDSA), Philadelphia, PA, October 29-November 1, 2009.

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Antiviral Treatment for Children With Influenza

What's the Evidence?

To the Editors:

Garg et al[1] have recently made a plea for the use of antiviral treatment for children affected or suspected of being affected with influenza, specially if they are at risk of complications or have been hospitalized, in line with recent Centers for Disease Control and Prevention, Advisory Committee on Immunization Practices and American Academy of Pediatrics recommendations.[2,3] They cite a Cochrane meta-analysis showing a reduction in illness duration and reduced incidence of otitis media in those aged 1 to 5 years.[4] Recently, the Cochrane Collaboration has released an updated review of unpublished regulatory information from trials of neuraminidase for influenza in adults and children. In their conclusions, they found a high risk of publication and reporting biases. For them, "the evidence supports a direct oseltamivir mechanism of action on symptoms but we are unable to draw conclusions about its effect on complications or transmission."[5] The difficulties to obtain full study reports from the manufacturer of oseltamivir and the implications for a change in the approach to systematic reviews have just been published online.[6,7] As most of the information about the efficacy of neuraminadase inhibitors in children with influenza at risk of complications or of hospitalized comes from retrospective and uncontrolled studies, I find unacceptably unfounded the strong recommendations made by the above organizations and find myself more comfortable with the conclusions adopted by the Food and Drug Administration and The Cochrane Collaboration. It is expected that transparent, properly designed and conducted, independent trials, instead of the induced force of habit, will help us in the future to obtain strong evidence to better guide our decisions for children infected with influenza.

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REFERENCES

1. Garg S, Fry AM, Patton M, et al. Antiviral treatment of influenza in children. *Pediatr Infect Dis J*. 2012;31:e43–e51.
2. Fiore AE, Fry A, Shay D, et al.; Centers for Disease Control and Prevention (CDC). Antiviral agents for the treatment and chemoprophylaxis of influenza—recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2011;60:1–24.
3. Committee on Infectious Diseases. Recommendations for prevention and control of influenza in children, 2011–2012. *Pediatrics*. 2011;128: 813–825.
4. Shun-Shin M, Thompson M, Heneghan C, et al. Neuraminidase inhibitors for treatment and prophylaxis of influenza in children: systematic review and meta-analysis of randomised controlled trials. *BMJ*. 2009;339:b3172.
5. Jefferson T, Jones MA, Doshi P, et al. Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children. *Cochrane Database Syst Rev*. 2012, Art. No.: CD008965. DOI: 10.1002/14651858.CD008965.pub3
6. Cohen D. Search for evidence goes on. *BMJ*. 2012;344:e458.
7. Doshi P, Jones M, Jefferson T. Rethinking credible evidence synthesis. *BMJ*. 2012;344:d7898

Reply:

Dr. Moral comments that most of the information on the efficacy of neuraminidase inhibitors for treatment of influenza virus infection in hospitalized children or children at increased risk of complications comes from retrospective and uncontrolled studies.[1] We agree with Dr. Moral that there is a paucity of clinical trials data to inform influenza antiviral treatment recommendations for children, especially those who are hospitalized or have underlying medical conditions. However, we disagree that observational studies should be disregarded as evidence to support guidance. While observational studies have inherent design limitations, they can inform clinical practice and public health, particularly when data from randomized controlled trials are unavailable, have not been conducted in certain high-risk groups, or are unethical to perform using a placebo group because antiviral treatment is recommended in the group under study. We support the need for additional studies to inform clinical practice and policy decisions including well-designed clinical trials and observational studies. However, while we await these data, we cannot ignore the fact that in the United States each year >100 children die from influenza and its complications[2–5] and an estimated 35,000 children are hospitalized,[6] with 11%–27% of hospitalized children having illness severe enough to require admission to an intensive care unit.[7] Among hospitalized children, 32%–75% have underlying medical conditions,[7] and chronic lung disease, neurological conditions, immunocompromised state and other high-risk conditions are associated with an increased risk of intensive care unit admission and death among children with influenza virus infection.[8–10] Two meta-analyses of oseltamivir clinical trials data, using the same databases but different methodologies, have concluded that early outpatient use of oseltamivir reduced hospitalizations and lower respiratory tract illness among healthy persons.[11,12] Furthermore, additional evidence supports a reduction in complications with early treatment.[13–15] When providing antiviral treatment recommendations, policy makers consider the total body of evidence that is available and account for potential benefits and risks, with the aim of reducing the morbidity and mortality associated with influenza illness, especially among those most at risk for severe illness. As new data become available, guidance can be updated and revised.

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REFERENCES

1. Moral L. Antiviral treatment for children with influenza: What's the evidence? *Pediatr Infect Dis J*. 2012;31:663–664.
2. Centers for Disease Control and Prevention. Influenza-associated pediatric deaths--United States, September 2010-August 2011. *MMWR Morb Mortal Wkly Rep*. 2011;60:1233–1238.
3. Cox CM, Blanton L, Dhara R, et al. 2009 Pandemic influenza A (H1N1) deaths among children–United States, 2009-2010. *Clin Infect Dis*. 2011;52(suppl 1):S69–S74.
4. Finelli L, Fiore A, Dhara R, et al. Influenza-associated pediatric mortality in the United States: increase of Staphylococcus aureus coinfection. *Pediatrics*. 2008;122:805–811.
5. Peebles PJ, Dhara R, Brammer L, et al. Influenza-associatedmortalityamongchildren-UnitedStates: 2007-2008. *Influenza Other Respi Viruses*. 2011; 5:25–31.
6. Reed C, Meltzer M, Kirley P, et al. Progress toward routine estimation of the seasonal burden of influenza in the United States. 49th Annual Meeting of the Infectious Diseases Society of America; October 22, 2011; Boston, MA. Abstract #1122.
7. Garg S, Fry AM, Patton M, et al. Antiviral treatment of influenza in children. *Pediatr Infect Dis J*. 2012;31:e43–e51.
8. Keren R, Zaoutis TE, Bridges CB, et al. Neurological and neuromuscular disease as a risk factor for respiratory failure in children hospitalized with influenza infection. *JAMA*. 2005;294:2188–2194.
9. Kumar S, Havens PL, Chusid MJ, et al. Clinical and epidemiologic characteristics of children hospitalized with 2009 pandemic H1N1 influenza A infection. *Pediatr Infect Dis J*. 2010;29:591–594.
10. Louie JK, Gavali S, Acosta M, et al.; California Pandemic (H1N1) Working Group. Children hospitalized with 2009 novel influenza A(H1N1) in California. *Arch Pediatr Adolesc Med*. 2010;164:1023–1031.
11. Hernán MA, Lipsitch M. Oseltamivir and risk of lower respiratory tract complications in patients with flu symptoms: a meta-analysis of eleven randomized clinical trials. *Clin Infect Dis*. 2011;53:277–279.
12. Kaiser L, Wat C, Mills T, et al. Impact of oseltamivir treatment on influenza-related lower respiratory tract complications and hospitalizations. *Arch Intern Med*. 2003;163:1667–1672.
13. The MIST (Management of Influenza in the Southern Hemisphere Trialists) Study Group. Randomised trial of efficacy and safety of inhaled zanamivir in treatment of influenza A and B virus infections. *Lancet*. 1998;352: 1877–1881.
14. Heinonen S, Silvennoinen H, Lehtinen P, et al. Early oseltamivir treatment of influenza in children 1-3 years of age: a randomized controlled trial. *Clin Infect Dis*. 2010;51:887–894.
15. Whitley RJ, Hayden FG, Reisinger KS, et al. Oral oseltamivir treatment of influenza in children. *Pediatr Infect Dis J*. 2001;20:127–133.

Acute Appendicitis Associated With Scarlet Fever

To the Editors:

Acute appendicitis associated with infectious disease is rare and such association is generally considered to occur coincidentally.[1] We treated a boy who developed acute appendicitis during the course of scarlet fever. Such association is rare, and the diagnosis and surgery may be delayed because the physicians tend to focus on the contagious disease.

The 6-year and 3-month-old boy developed sore throat and fever up to 40° 3 days before admission. In addition, a pruritic erythematous rash over the face, neck and body was noted. On admission, he appeared acutely ill. The body temperature was 37.6°, blood pressure 96/60 mm Hg, respiratory rate 20/min and pulse rate 104/min. Perioral pallor, coarse skin texture with diffuse scarletiniform rashes over the face, neck

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